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Introduction

Richard P. Schmidt, M.D.

A symposium, such as the International Conference on Vascular Disease of the Brain, may have several purposes. Foremost among these is a free exchange of ideas by investigators from related or seemingly unrelated disciplines. This may result, in turn, in the application of new thought or method to a problem. For the individual investigator, the most useful criticism often cannot appear in a printed report but is derived from personal contacts in the lobby or during a social hour. Several new projects are known to have been started as a result of arguments and lobby discussion at the Conference.

The more formal papers and recorded discussion serve an additional purpose of dissemination of information. For this reason, this Conference was "open" and attended by more than 400 interested physicians and scientists. Most of the audience were clinicians with an active interest in patient care who were anxious to learn of current research before publication. From their attendance, one may expect a more rapid transfer of investigative results into terms of diagnosis and treatment. Publication of the Proceedings as a supplement to a widely-distributed neurologic journal will give additional details of the studies and provide a source for those who could not attend the Conference.

The Chairman of the Planning and Publication Committee would like to take this opportunity to thank those who contributed to the success of this Conference. The other members of the Committee gave their time willingly and carried a large share of the burden of correspondence and editing. Dr. Augustus S. Rose, President of the American Academy of Neurology, provided wise counsel when needed but appropriately delegated authority to permit effective planning. Many others gave freely of advice and time. These include Dr. Adolph L. Sahs, who was chairman of an ad hoc committee which outlined the original conference proposal; Drs. Robert N. Baker, Oscar M. Reinmuth, and Peritz Scheinberg who arranged for the physical facilities with the Eden Roc Hotel; and Mrs. Doris McKinley, whose patient assistance was, as usual, felt in many ways. Finally, the participants deserve special commendation for their willingness to devote their time and energies to the Conference and to their manuscripts.

The United States Public Health Service through the National Institutes of Health, National Institute of Neurological Diseases and Blindness, made this Conference a reality by financial support. This agency is to be commended for stimulating interest and for continued support of research in cerebrovascular disease, which will be an increasing public health problem with our aging population.

Collateral circulation of the brain

Harry A. Kaplan, M.D.

THE ANASTOMOSES of the blood vessels of the brain are of two kinds: the normal blood vessel connections and those remaining as remnants of embryologic maldevelopment. Many can be visualized in the living by angiography, but others require demonstration only through anatomic studies. When the vascular system is examined in the complicatedly folded adult brain, a maze of vessels coursing in all directions can be seen. It is quite evident that, in order to present understandable data pertaining to this system and the anastomoses in particular, an orderly and methodical approach to the problem must be put forth. To do this, the brain and its vascular network will have to be reduced to a basic unit and the development to the final pattern followed through its various stages.

DEVELOPMENTAL ANATOMY

Embryologic studies[1,2] of the structure of the body demonstrate constant formation of new elements and dropping out of older ones. Some features in the developing embryo suggest that certain organs must pass through ancestral phases which will bear no relationship to the fully developed individual. The structural changes occur in order to adapt to new conditions. Some structures are functional only for a short period during development.

No human embryos have been studied in the very earliest stages of development. Therefore, these phases must be obtained from a study of lower animals. The vascular system has its origin in the mesenchyme distributed among various regions of the body. From the mesenchyme, hemangioblasts collect in clusters. Blood channels appearing first as solid cords develop by a flattening of the outer cells of the clusters to form endothelial cells. The cells of the inner part of the solid cord break down into a fluid plasma substance, some clumps remaining as hemocytoblasts. With the completion of the formation of blood channels, the hemocytoblasts begin to float in the primitive plasma and wander away to certain areas where more highly differentiated blood cells develop. At this early stage in the embryo, the vessels are growing merely to form a plexus; functional circulation of the blood does not take place until later.

The origin of the cells giving rise to blood vessels is still a speculative issue. However, certain excellent studies[3] have indicated that, from the first aortic arch and the dorsal aortae, capillary plexuses in specific locations grow upward to the base of the neural tube and then extend rostrally to the forebrain and caudally to the hindbrain. From the ventral aspect, the plexuses continue dorsally to surround the tube and ultimately to completely cover it. All blood vessels have their beginning in a multiple capillary anlage. The inner portion of the vascular meshwork lying against the brain wall remains of capillary dimensions, while its outer, or more superficial, layer, through a fusion of some of the channels and the dropping out of others, develops into larger, more direct channels.

In elaboration of the arterial system from the heart to the brain, 6 pairs of aortic arches develop as a result of interposition of the pharynx with its pouches between the heart and aortae. These connecting channels between the ventral and dorsal aortae develop in sequence but never are well developed all at the same time. The second aortic arch appears in the 2- to 3-mm. embryo. With the development of the third and fourth arches, the first arch involutes. The second arch disappears before the pulmonary, or sixth arch, becomes a continuous channel. With degeneration of the first 2 connecting aortic arches, the ventral root which fed them remains as the future external carotid artery and the dorsal aortic root into which they discharged,

as the internal carotid artery. A little later, the segment of the dorsal aortic root between the third and fourth arches drops out and the third aortic arch remains as the curved proximal part of the internal carotid artery. The part of the ventral aortic root lying between the third and fourth aortic arches forms the common carotid artery.

The data on the arterial development within the human head have been studied by several investigators. The following material has been taken from the work of Padget.[4]

The first stage in differentation of supply and drainage channels is noted in the embryo of 28 days and 4 to 5 mm. in length. The first and second aortic arches are in the early stages of involution, and the portions of paired dorsal aortae extending rostrally from the third arch, having the appearance of just emerging from a plexus, now represent the primitive internal carotid arteries. At the trigeminal ganglion, the internal carotid artery divides into 2 parts, 1 part being the primitive trigeminal artery plexus extending dorsally to join the longitudinal neural plexuses which have just become visible on the ventral aspect of the hindbrain, and the other extending rostromesially to connect through a plexiform channel with its fellow of the opposite side.

At the close of the "branchial" phase, in the embryo of 32 days of age and 7 to 12 mm. in length, the first notable cerebral branch of the internal carotid artery to make its appearance is the dorsal ophthalmic artery, which supplies a capillary plexus about the optic cup. From the primitive rostral division of the internal carotid artery arise several branches, the largest of which is the primitive anterior choroidal artery. Just distal to this branch are several twigs representing the middle cerebral artery stem. Before the rostral division of the internal carotid artery terminates at the olfactory pit, it gives off mesial twigs to the region of the future anterior cerebral artery. From the caudal end of the posterior communicating artery, 2 large branches emerge; 1 goes to the diencephalon to include the posterior choroidal artery directed toward the anterior choroidal artery. The trigeminal artery is dwindling in size. During this stage, the upper 6 intersegmental arteries forming the vertebral arteries develop crossing anastomoses and soon lose their attachments to the dorsal aortae.

The transition stage from "branchial" to "post-branchial" phase is seen in the 35-day embryo of 12 to 14 mm. in length. The primary cranial divisions of the internal carotid arteries may be described for the first time with respect to the definitive parts and collateral branches of the adult conformation. The anterior choroidal, middle cerebral, and anterior cerebral artery stems can now be visualized. The hyoid artery, with its carotid stem of origin now at the most cranial level of the hyoid bar, has given rise to an important collateral branch which passes through the stapes primordium between the first pharyngeal pouch and the seventh nerve and descends into the mandibular substance to join later with the ventral pharyngeal artery of the external carotid system. The cerebral arteries are now becoming much less plexiform.

In the embryo of 40 days of age and 16 to 18 mm. in length, the adult configuration of the cerebral arteries is becoming quite definite. When the embryo attains an age of 44 days and is 20 to 24 mm. in length, the proximal part of the posterior cerebral artery begins to form an angle of 90° with the internal carotid artery. The anterior communicating artery is now complete. The relationship of the posterior cerebral and mesencephalic arteries can be visualized. The fate of the temporary stapedial artery is revealed as its 2 major divisions, ventral and dorsal, are annexed by the internal maxillary and ophthalmic arteries, respectively. The part of the stapedial trunk lying above the recently completed anastomosis with the internal maxillary artery becomes the stem of the middle meningeal artery. The hyoid artery, which is the primitive vessel that has just served temporarily as the most proximal part of the stapedial stem, is retained also as the small caroticotympanic branch of the adult internal carotid artery.

The stems of origin of all cerebral arteries in the embryo of 52 days of age and 40 mm. in length are similar to those of the adult. The posterior cerebral arteries are as yet immature. The proximal segments of the pos-

terior cerebral arteries are large in both the embryo and newborn.

It becomes quite evident from this brief survey of the embryology of the vascular system what possible developmental defects may remain in the adult. Some of the persisting adult abnormal connections may be nonharmful or actual safety features when occlusion occurs in one of the main tributaries. However, other malformations such as the arteriovenous connections may produce results that are disastrous.

ADULT COLLATERAL ANATOMY

Extracranial collaterals. Anastomoses between the external and internal carotid systems occur at regions of exit from the skull of nerve elements closely related to the central nervous system, such as the eye, ear, and nose.

The ophthalmic artery has two main sets of branches, the ocular and orbital groups. As might be expected, the anastomoses in the regions of the eye and nose are between the orbital group of vessels from the ophthalmic artery of the internal carotid system and the external and internal maxillary branches to the face and nasal cavity, respectively, from the external carotid system. Angiograms in the living reveal a rather extensive collateral between the twigs of the internal maxillary artery and the ethmoid branches of the ophthalmic artery.

Collateral in the auditory region through the tympanic branch of the internal carotid artery and the internal auditory branch of the basilar artery connecting with branches of the external carotid system is normally minute. However, the persistence of the stapedial artery in the adult may theoretically afford a fair amount of collateral between the internal and external carotid systems in the region of the ear.

The stapedial artery normally present in the embryo forms when the dwindling of the second aortic arch leaves a stem, the hyoid artery, from the internal carotid artery. From the hyoid twig a collateral, the definitive stem of the stapedial artery, continues through the condensation of mesenchyme representing the stapes. After piercing the anlage of the stapes, it gives rise to three branches. The first of these is the ramus supraorbitalis. The common trunk then continues and divides into infraorbital and mandibular rami. The ventral pharyngeal artery, which may be considered as the primitive external carotid artery arising from the third aortic arch, grows forward to connect with the main stem of the stapedial just above the origin of the infraorbital and mandibular divisions. Blood then flows through the stapedial artery from both the internal and external carotid systems. Later, the stapedial artery separates at the stapes from its internal carotid source and then receives blood only from the newly connected ventral pharyngeal artery of the external carotid system. The trunk of origin of the infraorbital and mandibular rami above the connection with the ventral pharyngeal artery will become the future middle meningeal artery and the supraorbital segment, one of its branches. Later, the supraorbital branch divides, and its distal segment becomes annexed by the ophthalmic artery from the internal carotid to form the lacrimal artery. The proximal portion of the supraorbital division remaining connected to the external carotid system then becomes the anterior branch of the middle meningeal artery.

Extracranial-intracranial collaterals. Extracranial to intracranial arterial anastomoses result only from developmental abnormalities of the vascular system. These relatively rarely persisting connections occur in 3 main areas: the trigeminal artery in the region of the gasserian ganglion, the otic artery in the auditory area, and the hypoglossal artery in the vicinity of the twelfth cranial nerve.

The commonest of this group is the trigeminal artery. In the early embryo of approximately 28 days of age, a plexus of vessels can be seen to connect the dorsal aorta in the region of the first aortic arch with the neural vessels on the ventral aspect of the hindbrain near the gasserian ganglion. Before the joining of the hindbrain neural vessels to the proximal posterior cerebral arteries (posterior communicating arteries) of the forebrain and the development of the vertebral arteries, the trigeminal vessels are the main source of blood to the hindbrain. With the final development of the base vessels, the trigeminal arteries

recede. However, at times, the trigeminal artery may persist in the adult to form a large arterial connection between the internal carotid artery as it enters the region of the cavernous sinus and the upper third of the basilar artery.

Less often, large connecting vessels in the region of the auditory elements may persist from the embryo to connect the internal carotid artery in the base of the skull to the proximal portion of the basilar artery. An anastomosis between the internal carotid artery at the base of the skull and the vertebral artery in the region of the twelfth nerve is referred to as the hypoglossal artery.

Intracranial arterial anastomoses. The intracranial arterial anastomoses exist on the surface of the brain through interarterial connections of a well organized vascular system.[5] For the visualization of this pattern, the adult brain will have to be unfolded into its original neural tube state. Through thickening of the wall of the tube in 5 regions, a segmental structure is formed. The 5 segments, in a rostrocaudal direction, consist of the telencephalon, diencephalon, mesencephalon, metencephalon, and myelencephalon. From the dorsum of 3 of the segments—the telencephalon, mesencephalon, and metencephalon—suprasegmental cell masses referred to as the cerebral cortices, colliculi, and cerebellar cortices, respectively, develop. The rostral 2 segments, the telencephalon and diencephalon, comprise the forebrain, and the metencephalon and myelencephalon comprise the hindbrain. An interlinking network of fibers between cells and cell groups, together with the supporting structures, comprises the white matter. From the vascular injection studies, it becomes apparent that the arterial tree is primarily directed to cell areas.

The brain, viewed in its neural tube state, can be observed to receive its arterial blood flow from 2 main ventral sources. The forebrain receives its arterial supply from the internal carotid arteries through 4 large branches on each side and the mid- and hindbrain, from the vertebral basilar system through 4 large arteries on each side. Anatomically speaking, the 4 large branches of the internal carotid artery are the anterior cerebral, middle cerebral, anterior choroidal, and posterior cerebral arteries. From embryologic studies, the posterior cerebral artery has been found to arise from the internal carotid artery. Therefore, the posterior communicating artery is truly the proximal portion of the posterior cerebral artery. The terminal divisions of the basilar artery, usually referred to as the posterior cerebral arteries, are actually the mesencephalic vessels. These can be observed to continue about the midbrain to the suprasegmental colliculi. The mid- and hindbrains, through the mesencephalic, superior cerebellar, anterior inferior cerebellar, and posterior inferior cerebellar arteries are also supplied by 4 main vessels on each side. Each large vessel is identical, possessing medial and lateral perforating branches to the basal region, and distal perforating branches to the suprasegmental cell masses.

The arterial anastomoses of the brain occur in 3 main areas: [1] through connections of the large vessels at the base, [2] through the perforating branches to the basal nuclear masses, and [3] through the surface vessels on the suprasegmental cell areas. All collateral circulation of any significance takes place through arteries on the surface of the brain before their entrance into the substance of the nervous system. Collateral exists only between vessels irrigating adjacent neural areas. The arteries destined to a specific region of the neural tube may send branches on to an adjacent rostral segment but not to a more caudal segment.

At the base of the brain, large interconnecting channels permit collateral blood flow between the 2 internal carotids and the vertebral-basilar systems. These interconnecting channels make up the circle of Willis. The anterior communicating artery is the site of collateral between the 2 internal carotid artery systems. The junctions of the proximal posterior cerebral arteries (posterior communicating arteries) and the mesencephalic arteries (posterior cerebral arteries) are the sites of collateral between the arteries of the forebrain and hindbrain.

In the adult, the arteries making up the circle of Willis vary considerably in size. The 2 important linking channels of the circle of

Willis are the proximal portion of the anterior cerebral artery lying between the internal carotid and anterior communicating artery, and the proximal portion of the posterior cerebral artery lying between the internal carotid and the mesencephalic artery.

In a random group of 50 adult brains observed at autopsy, the arterial patterns making up the circle of Willis were studied; 44% of the group showed proximal posterior cerebral arteries of fine caliber and possibly inadequate for effective collateral blood flow. However, 16% had small proximal posterior cerebral arteries which appeared large enough possibly to carry sufficient blood for adequate collateral circulation. Therefore, 60% of the 50 cases appeared to have the greatest source of blood for the distal posterior cerebral artery from the basilar artery system; 4% had equally sized arteries in all parts of the circle of Willis, and 12% had large proximal posterior cerebral segments bilaterally, equal to the size of the distal posterior cerebral arteries. In this last group, the mesencephalic artery on 1 side was equal in size to the posterior cerebral artery; the other was smaller. A large proximal posterior cerebral artery on 1 side but a small artery on the opposite side were found in 18%; 6% showed a small proximal anterior cerebral segment on the side of the large proximal posterior cerebral artery. Finer variations of these gross patterns were also noted, but, for the most part, 60% of the group showed the proximal posterior cerebral arteries to be small and the distal posterior cerebral segment to appear as a continuation of the mesencephalic artery. In 40%, on either one or both sides, the distal posterior cerebral segment appeared to be of caliber equal to that of the proximal posterior cerebral segment. Rarely does one find the proximal anterior cerebral and proximal posterior cerebral artery segments small on the same side, but this I have seen. It would appear that adequate collateral might be present when one internal carotid artery is occluded if both proximal anterior cerebral artery segments are large or if the proximal posterior cerebral and mesencephalic artery on the same side are large. Fortunately, this appears to be the situation in more than 90% of the cases. Of course, many other factors, such as general blood flow and atherosclerotic changes, must be taken into account.

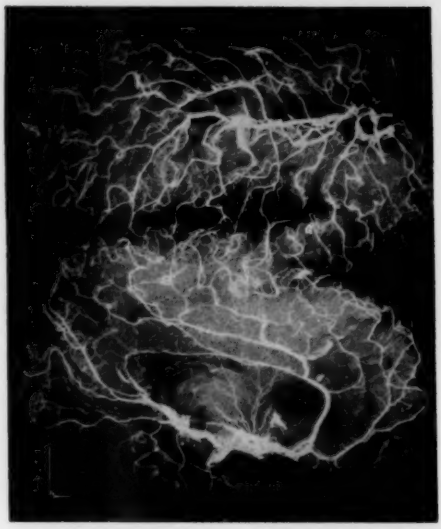

Fig. 1. Roentgenogram of arteries of forebrain injected with radiopaque medium. Lateral aspect of brain reflected dorsally to demonstrate anastomoses of peripheral segments of anterior, middle, and posterior cerebral arteries

The second important area of collateral deals with the small, but numerous, perforating branches to the basal cell masses.[6] Because of their size, any collateral from an equal size branch might well be adequate. Collateral between the large perforating vessel from the anterior cerebral artery, the anterior recurrent artery, and the large lateral perforating artery of the middle cerebral artery is occasionally present. These vessels supply nuclear cell areas in close approximation. Collateral is noted also between the perforating branches of the anterior choroidal and proximal posterior cerebral arteries and between the proximal posterior cerebral branches and the small perforators arising directly from the internal carotid artery. No significant collateral is found between the perforating arteries across the midline at the base.

Anastomoses are not common on the surface of the hindbrain. Single vessels arise from the basilar artery to divide ultimately into the various medial and lateral perforating twigs without connecting with any other branches.

The vessels do not cross the midline either on the surface or after penetrating the brain substance.

Similar anatomic relationships are possessed by 2 arteries of the forebrain and 2 arteries of the hindbrain. On the forebrain, the anterior choroidal artery and the posterior cerebral artery, including the proximal posterior cerebral artery, have extensive collateral in 4 main areas: [1] over the hypothalamus; [2] over the geniculate body; [3] in the choroid plexus of the lateral ventricle; and [4] on the surface of the mesial aspect of the temporal lobe. These arteries may vary markedly in size, and one may take over most of the supply of the other. On the hindbrain, the anterior and posterior inferior cerebellar arteries also have extensive collateral and may take over each other's areas of distribution. They have anastomoses over the base of the hindbrain, in the choroid plexus of the fourth ventricle, and over the surface of the cerebellum. The size or actual presence of one of these vessels may depend upon the size of the other.

The third area of collateral involves the surface anastomoses of the distal branches over the suprasegmental cell masses. The largest anastomoses appear to be between the peripheral segments of the large vessels arising from the main ventral sources. Some anastomoses are seen between the branches of a single large artery but much fewer than at the periphery of the main artery regions.

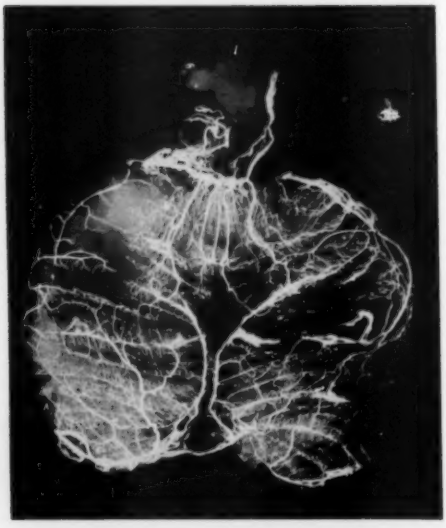

Fig. 2. Roentgenogram of arteries of cerebellum injected with radiopaque medium. Base of cerebellum reflected dorsally to demonstrate anastomoses of superior cerebellar and anterior and posterior inferior cerebellar arteries

On the forebrain, collateral is found on each hemisphere among the anterior cerebral, middle cerebral, and posterior cerebral arteries (Fig. 1). The greatest collateral appears between the anterior cerebral and middle cerebral arteries and between the middle cerebral and posterior cerebral arteries. Anastomoses are found in varying extent across the midline on the dorsum through connections between the two anterior cerebral arteries and between the perforating branches of the posterior cerebral artery in the vicinity of the pineal body and choroid plexus.

On the hindbrain, collateral is quite marked over the surface of the cerebellar hemispheres. The superior cerebellar artery sends branches rostrally over the posterior colliculi of the midbrain to anastomose with branches of the mesencephalic vessels. The arteries over the suprasegmental cell masses of the hindbrain have more anastomoses with each other than those over the forebrain. Extensive collateral exists among the superior cerebellar and anterior and posterior inferior cerebellar arteries (Fig. 2). Anastomoses across the midline are present between the superior cerebellar arteries in the region of the anterior medullary velum. In the region of the fourth ventricle, anastomosis is present between the two posterior inferior cerebellar arteries. At times, a large crossing vessel is found which seemingly allows for the artery of one side to irrigate much of the base of the cerebellum bilaterally. Usually, in these cases, the posterior inferior cerebellar artery of one side is small or absent and a large anterior inferior cerebellar artery is seen on the other side.

SUMMARY

The collateral circulation to the brain exists in 3 main areas: [1] through extracranial arterial connections; [2] through developmental extracranial to intracranial persisting arteries; and [3] through intracranial cerebral arterial anastomoses. The intracranial cerebral

arterial collateral occurs in 3 main areas: [1] through connections of the large base vessels (circle of Willis); [2] through connections between the perforating vessels to the basal cell masses; and [3] through interarterial connections on the suprasegmental areas of the brain. All collateral occurs on the surface of the brain.

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Discussion of "Collateral Circulation of the Brain"

Henri vander Eecken, M.D.

Dr. Kaplan's excellent review of this subject is of great importance to all those who are interested in cerebrovascular diseases. We are grateful, indeed, for his own original contributions in this field. It is not easy to discuss such a beautifully illustrated and logical paper.

Dr. Kaplan started by emphasizing that the direction and position of the cerebral arteries are governed by the anatomic location of the cellular masses; vessels arising from 2 main sources give off perforating branches to the deep cell masses and course further over the surface to irrigate dorsal or suprasegmental regions. This simple design is found throughout the brain and persists despite the complex developmental readjustment of the components of the encephalon.

In connection with this point, I would like to recall the terminology introduced by the outstanding French neurologist, Charles Foix,[1] for the branches of the vertebral-basilar system —paramedian, short circumferential, and long circumferential (or the cerebellar arteries). All the cerebrovascular system seems, in fact, to conform to the same general pattern.

Fig. 1. Precuneal artery arising from contralateral anterior cerebral artery

Dr. Kaplan has reviewed the classic embryologic notions which are indispensable in the understanding of the evolution of certain anastomoses and anomalies.

The adult arterial collateral anatomy is further divided in extracranial, extracranial-intracranial, and intracranial collaterals. One must conceive indeed that the arterial cervicocerebral network, constituted on the one hand by the carotid arteries and the vertebrobasilar trunk, with their branches of division, and on the other hand by the anastomoses which connect them in the cervical region, on the base of the skull and on the surface of the brain, makes up a whole. The first device works in the normal circulation, while the second, which is also individually more variable, interferes rarely in normal conditions.

Concerning the extracranial collaterals, I would like to add to those already mentioned by Dr. Kaplan the anastomoses between the occipital artery of the external carotid artery with muscular twigs of the vertebral artery and anastomoses between the frontal branch of the superficial temporal artery with the frontolateral branch of the ophthalmic artery.[2–6] These connections are, in general, less efficient than those in the nasal and orbital regions but certainly more efficient than those in the auditory region.

As far as the stapedial artery is concerned, Kluyskens of the Otorhino-laryngology Department of Ghent made a special study (to be

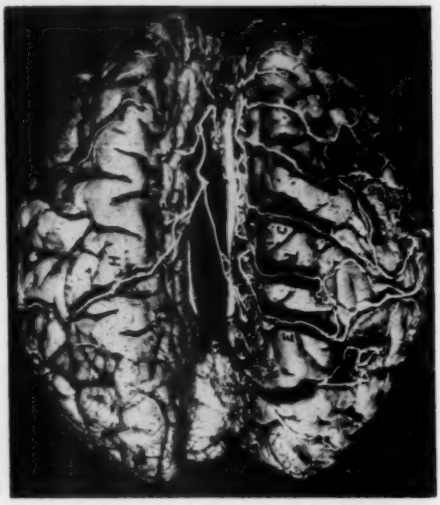

Fig. 2. Right precuneal artery originating from left callosomarginal artery

published) in the course of stapes mobilization operations in 250 adults and found, in each case, a very small arteriole without any possibility of providing eventually a vicarious circulation for the brain.

We have no personal experience with the extracranial-intracranial collaterals—remnants of the primitive trigeminal, otic, and hypoglossal arteries. However, from the literature, these anastomoses, even the trigeminal artery, seem very rare in the adult human. Tönnis and Schiefer,[5] in a study of 1,657 cases by way of serial angiograms, found only 8 carotid-basilar anastomoses, which is not even 0.5%.

With regard to the intracranial arterial anastomoses, I wish to point to the excellent suggestion of Dr. Kaplan in referring to the distal divisions of the basilar artery as the mesencephalic arteries and to the posterior communicating arteries as the proximal portion of the posterior cerebral arteries. Such a terminology corresponds on the one hand with the irrigation area and on the other hand with the morphogenesis, since de Vriese[7] has demonstrated that phylogenetically the posterior cerebral arteries have their origin in the internal carotid arteries.

Dr. Berry is better qualified to comment further on the circle of Willis and on its perforating ganglionic branches. I would only ask Dr. Kaplan, if and to what extent, the caliber of the anterior communicating artery and of the middle cerebral artery plays a role in the diameter relationship between the proximal portions of the anterior and posterior cerebral arteries? Dr. Kaplan indeed mentioned that if one of the 2 vessels—the proximal portion of the anterior or posterior cerebral artery (posterior communicating artery)—is small, the other will be large.

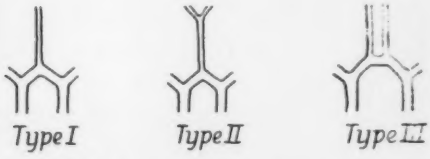

Fig. 3. Origin of the anterior cerebral artery: Morphologic types considered as remnants of arterial system of embryonic encephalon

Fig. 4. Type I morphologic structure: 2 anterior cerebral arteries join to form 1 anterior cerebral artery on inferior surface of brain of Macacus rhesus.

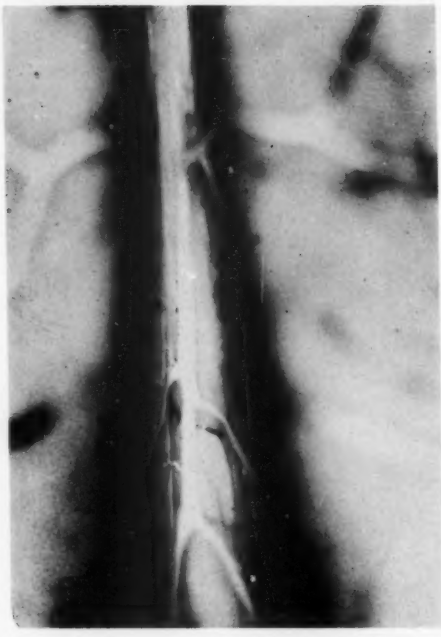

Fig. 5. On superior surface of brain seen in Figure 4, 1 anterior cerebral artery gives off branches for both hemispheres.

As far as the peripheral arborization is concerned, I wish to draw your attention to relatively frequent anomalies of the anterior cerebral artery, which can play a role in limiting the areas of softening caused by an arterial occlusion. In a series of 80 normal adult and 10 normal newborn children's brains, we found in 12 cases a precuneal artery arising from the contralateral anterior cerebral artery. In a 2-month-old child's brain (Fig. 1), a right precuneal artery originating in the posterior part of the contralateral pericallosal artery was seen. Figure 2 shows a right precuneal artery originating from the left callosomarginal artery in a 40-year-old man's brain. In 4 cases, a medial arterial pericallosal artery was found next to the 2 "classic" pericallosal arteries and in 1 case, only a single pericallosal artery. In 8 cases, a posterior pericallosal artery originated from either the contralateral pericallosal or a medial pericallosal artery. We considered these anomalies to be remnants of the formerly far more complete arterial system of the embryonic encephalon. This interpretation seems to be confirmed by some comparative anatomic studies in brains of mammals, where we found, as have other writers, roughly 3 morphologic types (Fig. 3).

The structure of Type I (Fig. 4), 2 anterior cerebral arteries joining to form further 1 anterior cerebral artery, is demonstrated here on the inferior surface of the brain of a Macacus rhesus. In Figure 5, one observes on the superior surface 1 anterior cerebral artery giving off branches for both hemispheres. This type is also present in the white mouse, guinea pig, rabbit, cat, mole, weasel, hedgehog, squirrel, lemur, otter, pig, and other animals.

Type II (Fig. 6) is found in the horse, where 2 anterior cerebral arteries fuse to form 1 short trunk, which divides into 2 branches, each irrigating 1 hemisphere.

Type III (Fig. 7), 2 anterior cerebral arteries connected at the base of the brain by an anterior communicating artery, as in the

Fig. 6. Type II morphologic structure: in horse, 2 anterior cerebral arteries fuse to form 1 short trunk, which divides into 2 branches, each irrigating 1 hemisphere.

Fig. 7. Type III morphologic structure: on inferior cerebral surface of young elephant, 2 anterior cerebral arteries are connected at base of brain by anterior communicating artery.

human being, is demonstrated here on the inferior cerebral surface of a young elephant. It is also present in the deer, ox, fox, orang-outang, and other animals.

As to the collaterals between the encephalic surface vessels, there are, indeed, a great number of anastomoses of sufficient caliber for eventual serviceable collateral blood supply in the border areas of the 3 cerebral and cerebellar arteries. While efficient anastomoses between 2 branches of one and the same cerebral artery are not common, these are less exceptional between the branches of a cerebellar artery.

However, the number, diameter, and location of these encephalic leptomeningeal anastomoses at the demarcation zones between the main encephalic arteries show large individual variations. The highly variable nature of these anastomoses in the human adult brain is, in our opinion,[8,9] due to a regression to a greater or lesser degree of the more complex vascular system of the embryonic and fetal encephalon.

As regards the deep perforating branches at the base of the brain and those of the cortical leptomeningeal arteries, like Dr. Kaplan, we rarely succeeded in our studies[9] with the corrosion technic after latex injection (in either their proximal or distal segments) in finding an anastomosis of significant size after the small branches entered the cerebral substance.

In conclusion, let us still bear in mind that the efficiency of this collateral arterial device "of relief," which shows morphologic variations from one individual to another, depends entirely on the functional state of the crucial moment.

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Discussion of "Collateral Circulation of the Brain"

Richard G. Berry, M.D.

We have ample embryologic, phylogenetic, and adult morphologic evidence, as pointed out by Dr. Kaplan and Dr. vander Eecken, that potential collaterals exist between the internal and external cranial circulations and between the major vessels supplying the brain through its leptomeningeal anastomoses. In his monograph, Dr. vander Eecken[1] has shown the potentialities of the leptomeningeal anastomoses in limiting the extent of an infarction. As Gillilan[2] has emphasized, the internal-external collaterals are less effective the more proximal the occlusion. We may question what significance these variations and potential collaterals have for the clinician and the patient suffering vascular occlusion.

Many anatomic, pathologic, and physiologic factors can be demonstrated or assumed to influence the extent and severity of an area of softening after occlusion of a major cerebral vessel. The degree of recovery from a stroke probably depends to a significant extent upon these factors.

Our efforts have been directed toward an analysis of the variations in the circle of Willis which may have significance in defining the amount of damage inflicted on the human brain by occlusive vascular disease. We have assumed that normal flow of blood depends to a large extent on the morphologic makeup of the circle of Willis, providing as it does the only source of blood supply to the human brain. Other anatomic factors, such as the leptomeningeal anastomoses between the major vessels at their distal portions, are limiting features in "containing the extent" of the damage. Pathologic alterations in the individual vessels, the systemic circulation, and the oxygenation of blood will alter not only the extent of damage but the availability of functional collateral circulation. Secondary effects of the infarction, notably cerebral swelling and diminished respiratory excursion with complicating pneumonia or pulmonary edema, establish a cycle of poor oxygenation and further swelling. One of the principal reasons for emphasizing such secondary effects is my impression in several cases that there was a venous distribution of lesions.

In outline form, these factors can be summarized thus:

I. Possible sources of collaterals
  A. Anatomic
    1. Potential collaterals
      a. Circle of Willis (normal)
      b. External-internal carotid anastomoses
        (1) Middle-anterior meningeal
        (2) Facial group
        (3) Anterior choroidal-posterior cerebral
      c. Superficial cerebral
        (1) Anterior-middle-posterior cerebral
        (2) Basilar-posterior cerebral
    2. Variations of these anatomic factors
      a. Variations of circle of Willis in normal brains

II. Some factors delimiting an area of softening
  A. Morphologic factors
    1. Variations in circle of Willis and other anastomoses
    2. Location of occlusion
    3. Arteriosclerosis of circle, superficial, and parenchymal vessels
    4. Brain swelling affecting large arteries

VARIATIONS OF CIRCLE OF WILLIS

	Normal brains (350)	*Softening* (194)	*Intracerebral hemorrhage* (61)
Normal circle			
Aneurysm included	–	33%	57%
Aneurysm excluded	52%	32	42
String-like vessels	26	43	23
Embryonic posterior cerebral	15	29	15
Duplicate vessels	9	13	11
Triple anterior cerebral	8	6	7
Absent posterior communicating	0.6	1.5	0
Fusion anterior cerebral	1.7	1	0
Aneurysm	–	6	23
Multiple anomalies	23	26	15

by shift, and compression of parenchymal arteries and veins

B. Physiologic factors: blood pressure; cerebrovascular resistance; systemic blood oxygenation; perivascular nerves; activity of neurons (?)

C. Pharmacologic factors: CO_2; metabolites

D. Temporal factors: age of patient; time to develop occlusion; time to develop anastomoses

Our investigation depends necessarily on a study of selected postmortem specimens. In relation to cerebral softening, adequate examination of the major vessels in the neck has been lacking.

Within the limits of this selection, the anatomic variations in the circle of Willis have been determined in normal brains in order to establish a base line for statistical comparison with a series of brains with vascular disease.[3] Only about one-half of the circles are normal in the sense of a configuration one would expect from textbooks. Absent component parts are rarely found and, when described, are suspect as artifacts, in our experience.

The most frequent and potentially important variations noted in normal brains are string-like component parts of the circle. These occur, either alone or combined with other variations, in about one-fourth of the circles of Willis. Although some of these string-like vessels may appear as fibrous threads, microscopic examination shows them to be patent. Nevertheless, the potential value of these vessels as collaterals in an emergency should be questioned, especially if the small lumen is further compromised by an atheromatous plaque.

In about one-seventh of normal brains, a persistence of the embryonic derivation of the posterior cerebral artery from the internal carotid occurs as a variation. This implies that the entire hemisphere is dependent upon the internal carotid artery.

A significant difference is present between brains with cerebral softening and those with no vascular disease or with massive intracerebral hemorrhage (see table). Abnormal circles are more common in the former than in the latter. This principal abnormality is in the incidence of small or attenuated vessels. In those brains with softening, 49% had string-like component parts of the circle of Willis either alone or in combination (including 2 cases of absent posterior communicating vessels). This is almost twice the incidence of string-like vessels (26%) in normal brains. When the figures are analyzed, the findings are essentially the same whether areas of involved vascular supply or occluded and non-occluded major vessels are compared. Abnormal circles are more frequent in brains with gross softening than in normal brains in each category. Persistent embryonic derivation of the posterior cerebral artery from the internal carotid is also significantly more frequent in brains with encephalomalacia.

String-like attenuated vessels, most fre-

quently those connecting the vertebral-basilar with the internal carotid, are usually patent, but their small lumens raise the question of their adequacy in the event of sudden emergency when occlusion takes place elsewhere.

In addition to congenital lumen adequacy as a variation in the circle, another limiting factor is the pathologic condition of narrowed lumen secondary to arteriosclerosis, especially as arteriosclerosis tends to be present at bifurcations and origins of vessels. We lack definitive study of this important process.

Analysis of individual instances of softening wherein grossly significant vascular insults occur is rewarding in some cases but serves to emphasize the fact that many other variables must be considered in addition to morphologic variation in the circle of Willis. In general, there is a significant correlation between the incidence of attenuated or string-like arteries and softening, but the significance is often not apparent in the analysis of an individual specimen. It is easier to find single areas of softening which seem unrelated to a specific vascular variation than to demonstrate instances of occlusive disease wherein such a variation of the circle is obviously important in location and extent of an area of softening.

Especially significant in the effects of occlusion of a large artery must be the anastomoses over the surface, so nicely demonstrated by Dr. vander Eecken and Dr. Kaplan.

We can summarize by saying that the blood flow to the brain depends on the circle of Willis. The circle of Willis is extremely variable as a potential anastomotic channel. The incidence of variations is higher in those brains with gross evidence of softening than in those brains with no softening. This difference between normal and encephalomalacic brains is due to a twofold increase in string-like or attenuated vessels and, to a lesser extent, persistent embryonic derivation of posterior cerebral arteries. The presence of string-like or, rarely, absent component parts of the circle in normal brains, even though severely arteriosclerotic, means that the function of the circle as an anastomosis was not called into being during life.

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Cerebrovascular disease

VII. A study of etiologic mechanisms

A. B. Baker, M.D., Ph.D., and A. Iannone, M.D.

WITH THE INCREASING INTEREST in cerebrovascular disease, renewed effort has been made by many investigators to discover factors that may play a role in the development of this degenerative process of the cerebral vessels. To date, the observations published have not been consistent. It was therefore felt worthwhile to restudy the many suggested etiologic factors on a large series of unselected cases in which a uniform coding system was used to record the degree and extent of the cerebrovascular changes.

In discussing cerebrovascular disease, it is imperative that one first define the scope of the study. Actually, there are 3 distinct groups of cerebral arteries, each differing from the others in the nature of its degenerative process. The first group of arteries are those of the circle of Willis and the larger vessels over the surface of the brain.[1] These arteries vary from 600 to 2,500 μ in diameter. The degenerative process implicating these vessels is predominantly limited to the intima and is the process usually described in the literature as atherosclerosis. The second set of vessels is the intracerebral arteries ranging from 150 to 600 μ in diameter. The chief degenerative change in these arteries is limited to the adventitia, which undergoes proliferation and ultimately replaces the entire vessel wall.[2] The arterioles, the third group of vessels, have a size of 150 μ or less. The chief degenerative change in these vessels is limited to the media and consists of a progressive medial fibrosis.[3]

Any study of cerebrovascular disease must, therefore, consider carefully the artery size and the type of degenerative change characteristic for the vessel. The present study is limited to the changes in the larger arteries of the circle of Willis, since this is the process that has stimulated the most interest in relation to the problem of cerebrovascular disease. In the present study, 1,175 consecutive cases were surveyed employing a simple coding system for the cerebral arteries.[4] The one which was adopted is a coding system in which the different degrees of atherosclerosis are sharply demarcated from one another and are fairly easy to duplicate by other investigators. The degrees of atherosclerosis were graded from 1 to 4+:

- 1+: Opacity to very thin plaques involving only a small part of vessel circumference. No lumen narrowing
- 2+: [A] Thin plaques involving more than half the vessel circumference with minimal lumen narrowing. [B] Small, thick plaques which produce less than 25% lumen narrowing
- 3+: [A] Thin plaques involving the entire circumference with mild lumen narrowing. [B] Localized plaques producing 25 to 50% narrowing
- 4+: [A] Very thick plaques involving the entire circumference with moderate or marked lumen narrowing (pipestem). [B] Localized plaques resulting in more than 50% lumen narrowing.

A total of 28 different areas along the circle of Willis were graded as to the degree of atherosclerotic change present (0 to 4+). The total numerical value for the atherosclerotic process was determined by multiplying each of these 28 areas by the degree of atherosclerosis present in each area and adding the total. Since there were 28 areas along the circle of Willis and the most severe atherosclerosis was 4+, the maximum total of involvement was 28×4, or 112. However, none of the cases showed such a high total score, since many arteries of the circle of Willis are minimally involved even in the presence of severe changes. Based on the total points of

atherosclerosis, our cases were then divided into 4 groups: no changes, minimal changes, moderate changes, and severe changes.

NATURE OF THE DEGENERATIVE PROCESS

Most authors agree that atherosclerosis denotes a pathologic process primarily affecting the intima of larger arteries, characterized by focal thickenings in which stainable lipids can be demonstrated in and between the cellular elements. Studies of larger series of cases have shown at one extreme almost exclusive fibrous composition with no or only minimal quantities of lipid material and, at the other, lesions with lipid accumulations of massive proportions. Based on these widely different appearances, two schools of thought have developed regarding the primary nature of this atherosclerotic process; one group of investigators believes that the earliest and primary change is an intimal thickening due to an increase in connective tissue.[5–7] The deposition of fat within the thickened intima would then be secondary and therefore variable in its presence and intensity. The second theory is that atherosclerosis is primarily a disease of fat absorption and that lipid material, once deposited in the intima, stimulates the growth of connective tissue as the first step in the formation of an atheromatous plaque.[8–11]

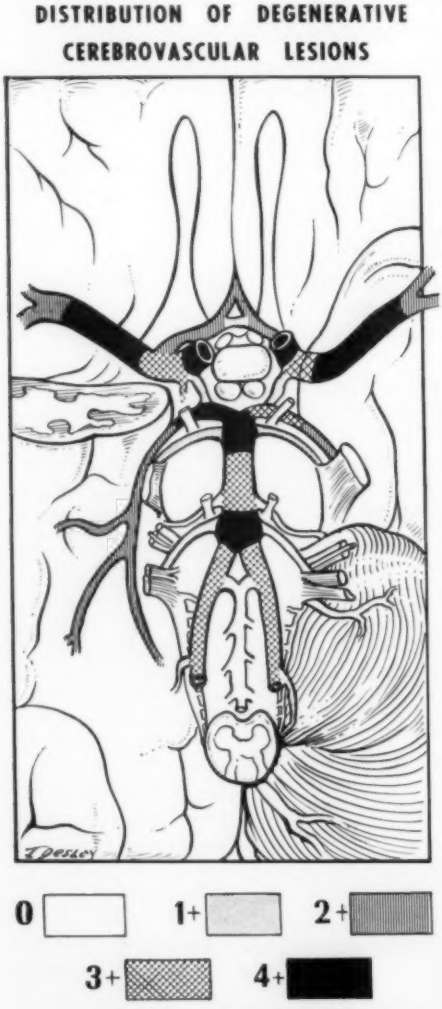

Fig. 1. Distribution of degenerative lesions in large cerebral arteries in 1,175 consecutive autopsies. Severity of lesions is illustrated by intensity of shaded areas.

Our observations on the larger cerebral arteries favor the first of these two views. The most consistent and earliest vessel change was the deposition of a light-staining material within the intima which separated the endothelial lining from the elastica interna. This material at no time could be stained with fat stains but soon assumed a strand-like structure that accepted connective tissue stains. Intimal connective tissue proliferation was often the only tissue change observed and, in many vessels, was present with no associated fatty deposits. It was the predominant type of alteration observed within many of the smaller arteries of the circle of Willis. Even in the larger arteries where fatty deposits were often encountered, connective tissue proliferation within the intima was often seen in areas where no fatty substances were present. Fatty deposits in cerebral arteries appeared to be a late occurrence rather than a primary event.

The nature of this pathologic process is extremely important in the study of cerebrovascular disease. If the intimal connective tissue changes are the earliest and often the only changes that occur, a study of this process based on fat stains alone would be very inadequate, since it would miss many of the

existing lesions. This must be kept in mind in evaluating experimental results based on such a staining technic.

MECHANICAL STRESS AND ATHEROSCLEROSIS

It has been postulated that mechanical tension and vibration exerted at the sites of vascular fixation or vibration can result in a loosening of the ground substance of the intima, thus favoring a reactive intimal proliferation.[11–13] Such mechanical stresses could also be exerted on the vascular wall by the impact of the pulse wave as well as by the blood current, such as occurs in hypertension.[14–16] In order to study the significance of these factors, a survey was made in our cases of the location of the most frequent and severe lesions and of the possible influence of hypertension on the severity of the atherosclerotic changes.

Location of the atherosclerotic changes. A study of the location and intensity of the atherosclerotic process was carried out in 1,175 cases using the coding system described (Fig. 1). The 4 areas along the circle of Willis most intensely involved were the upper and lower regions of the basilar arteries, the internal carotid arteries up to the trifurcation, the first third of the middle cerebral arteries, and the first part of the posterior cerebral artery on the right side. Although some of these involved regions are in proximity to vessel bifurcations, this is not uniformly true. The lesions in the upper basilar and internal carotids seem to occur at points of bifurcation where mechanical stress might well play a role. However, the lesions of the middle and posterior cerebral arteries, which were equally severe, did not occur at points of maximum stress but involved these vessels beyond the point of bifurcation. Uniformly, the smaller arteries such as the anterior and posterior communicating and cerebellar arteries revealed the mildest changes regardless of their relationship to points of fixation or branching. This would suggest that the size of the vessel, rather than its fixation, played the most important role in this degenerative process. It is possible that the larger arteries are subjected to greater intravascular stress and more readily develop degenerative changes.

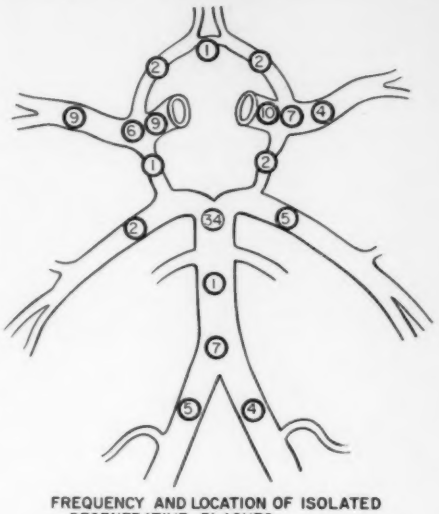

Fig. 2. Location of initial plaques of atherosclerosis along circle of Willis

Adams and vander Eecken[17] believed that the earliest atherosclerotic changes formed at the junction of arteries and then coalesced to involve more distant areas of the vessel wall. To further check this observation, we surveyed our cases for the location of isolated plaques in order to determine the location of the earliest degenerative changes (Fig. 2 and Table 1). Although isolated plaques were often present at the points of bifurcation of the vertebral and internal carotid arteries, many lesions appeared in areas not related to vessel bifurcation—for example, midportion of the basilar artery, anterior third of the middle and posterior cerebral arteries, and posterior part of the anterior cerebral arteries.

TABLE 1
LOCATION OF ISOLATED PLAQUES IN 1,175 CASES

Location	*Frequency of involvement*
Internal carotid artery up to and at trifurcation	13%
Vertebrals at junction of basilar	9
Middle basilar	7
Posterior cerebral	10
Middle cerebral	3

TABLE 2
HEART WEIGHT AND ATHEROSCLEROSIS IN 656 AUTOPSY CASES

Age group	Heart weight under 450 gm. Number	Total	%	Heart weight over 450 gm. Number	Total	%
No atherosclerosis						
31–40	14	16	87	2	3	66
41–50	34	41	83	11	14	79
51–60	57	76	75	28	46	61
61–70	57	100	57	26	68	38
71–80	47	113	42	20	72	28
81–90	16	67	24	4	27	15
91 –	1	12	8	0	0	0
Severe atherosclerosis						
31–40	0	16	0	1	3	33
41–50	3	41	7	2	14	14
51–60	9	76	12	15	46	33
61–70	36	100	36	40	68	59
71–80	60	113	53	50	72	70
81–90	51	67	76	22	27	81
91 –	11	12	92			

Blood pressure and atherosclerosis. It is a commonly accepted medical concept that hypertension will hasten the atherosclerotic process.[14–16] Many investigators believe that the heightened intravascular tension results in a mechanical stress exerted on the vessel wall and plays an important role in the internal changes which comprise this degenerative process. To check these observations, we studied the possible influence of hypertension on cerebral atherosclerosis in 656 consecutive autopsies. The heart weight was used as the most reliable criterion of hypertension. A heart weight of over 450 gm. was used as our index of hypertension. It would appear that hypertension does play a role in cerebral atherosclerosis. In all age groups, patients with heart weights of more than 450 gm. had more intense cerebrovascular changes (Fig. 3 and Table 2). The difference in severity of cerebral atherosclerosis was as high as 30% in the sixth decade of life.

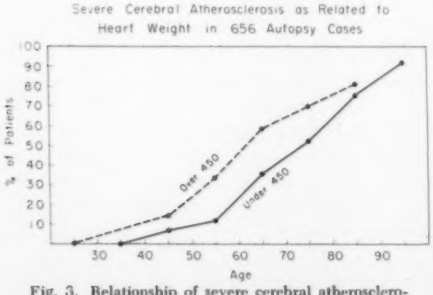

Fig. 3. Relationship of severe cerebral atherosclerosis to heart weight in 656 consecutive autopsies

One must conclude from these observations that mechanical stress may play a role in influencing the rate and intensity of cerebral atherosclerosis. It would appear that the most important mechanical factor is the increased stress exerted upon the vascular wall, as in hypertension. The stresses applied by the blood current upon sites of vascular fixation or bifurcation appear to play a much less important role in this process.

AGE AS RELATED TO ATHEROSCLEROSIS

Many investigators have suggested that atherosclerosis is the result of an aging process which may be modified by vasoactive factors.[18–20] There is no doubt that cerebral atherosclerosis gradually increases with age. A study of 1,175 cases shows that the atherosclerotic process begins as early as the second decade of life and rapidly increases in frequency after the third decade. However, within the ninth decade of life, 5% of the patients showed no cerebral atherosclerosis (Table 3). Since cerebral atherosclerosis occurs in so many young individuals and is absent in many older patients, it is apparent that age alone is not specifically related to this process. Apparently, atherosclerosis is a disease of blood vessels produced by a chronic process which requires years for its development. It appears more commonly in older individuals where the causative factors have ample time to produce the changes. Age therefore would be an accompanying factor rather than an etiologic agent in this degenerative process.

SEX AS A FACTOR IN ATHEROSCLEROSIS

Based on studies of coronary artery disease, it has been suggested that endocrine factors may be important in atherosclerosis, since this degenerative process in the coronary vessels

TABLE 3
CEREBRAL ATHEROSCLEROSIS IN 1,175 CASES BY DECADES

Age group	No atherosclerosis			Severe atherosclerosis		
	Number	Total	%	Number	Total	%
0–10	107	107	100	0	107	0
11–20	30	33	91	0	33	0
21–30	32	33	97	0	33	0
31–40	50	60	84	4	60	7
41–50	84	116	72	6	116	5
51–60	118	232	51	36	232	16
61–70	80	287	28	107	287	37
71–80	30	272	11	156	272	57
81–90	6	120	5	93	120	77
91 –	1	15	7	13	15	87

seems to be more frequent in males than in females.[10] No such comparative studies in the two sexes have been reported for the cerebral arteries. In smaller series on the cerebral vessels, it appears that the sex difference apparent in atherosclerosis of the coronary arteries does not carry over, even though the pathologic process appears to be similar. We believed, therefore, that a study of the sex factor in cerebral atherosclerosis in a large consecutive series of cases might prove of value in elucidating the role of endocrine factors in the cerebral degenerative process. We have tabulated (Table 4) the cerebrovascular changes in both males and females in a series of 1,175 consecutive autopsy studies. It is readily apparent that there is little difference between the two sexes when studied in each decade. Certainly, some of our decade groups had a limited number of cases for comparison. However, in those groups where the atherosclerotic process was most prevalent, sufficient material was available to indicate that males are not more susceptible to cerebral atherosclerosis than are females.

These studies raise considerable doubt as to the significance of endocrine factors in cerebral atherosclerosis. It has been postulated that the actual thrombotic process that results once the initial intimal degeneration occurs may be less prevalent in females than in males, thus giving the erroneous impression that cerebral atherosclerosis itself is also less prevalent. However, a survey of our cases for the frequency of acute cerebrovascular insults due to the acute thrombotic process does not substantiate this conclusion. The two sexes showed an equal number of acute vascular occlusions; even this thrombotic process is probably not influenced by endocrine factors.

NUTRITION AS A FACTOR IN CEREBRAL ATHEROSCLEROSIS

In spite of rapid developments in our knowledge concerning nutrition, it is surprising that very little definite information is available concerning the influence of nutrition upon the arteries. A considerable amount of clinical and pathologic data exists that tends to suggest that obese individuals are more prone to atherosclerosis.[21–23] However, this concept is not universally accepted, and some observers have pointed out that remarkably soft vessels may be found in obese persons.[24] It has also been suggested that thin, undernourished persons

TABLE 4
SEX AS RELATED TO CEREBRAL ATHEROSCLEROSIS IN 1,175 AUTOPSY CASES

Age group	No atherosclerosis					
	Male			Female		
	Number	Total	%	Number	Total	%
0–10	59	59	100	34	34	100
11–20	11	13	85	6	11	54?
21–30	17	17	100	11	12	92
31–40	26	31	84	17	21	81
41–50	37	53	70	44	55	80
51–60	70	133	53	47	75	60
61–70	51	163	31	31	98	32
71–80	24	133	18	12	123	10
81–90	3	59	5	5	57	11
91–						
	Severe atherosclerosis					
0–10	0	0	0	0	0	0
11–20	0	0	0	0	0	0
21–30	0	0	0	0	0	0
31–40	1	19	3	3	21	7
41–50	4	53	8	2	55	4
51–60	25	133	19	8	75	11
61–70	64	163	39	45	98	46
71–80	68	133	51	78	123	63
81–90	50	59	85	41	57	72
91 –	4	4	100	8	10	80

tend to have somewhat less atherosclerosis.[8,23]

Because of the importance of this factor and the lack of agreement in the literature, our cases were surveyed for the effect of weight upon the atherosclerotic changes in the cerebral vessels. The standards of the Metropolitan Life Insurance Company were adopted for the determination of weight standards. Table 5 shows that weight apparently has no influence on cerebral atherosclerosis. In all age groups, practically the identical percentage of individuals was free of atherosclerosis regardless of weight. Weight also seemed to play little role in the production of severe atherosclerotic changes. Although in the sixth and seventh decade it would appear that overweight individuals more frequently had severe changes, in the fifth and eighth decades this process was apparently reversed and the undernourished patients had more severe changes. No doubt this variability was due to an inadequate number of cases.

It has been suggested that diabetes may play a role in accentuating the atherosclerotic process. Our material contained too few cases to allow definite conclusions. Only 16 diabetic patients appeared in our study. Of these, 1 had no changes, 4 had mild changes, and 11 showed moderate to severe changes. Diabetes does not seem to accentuate the atherosclerotic process, but our cases are too few to offer any conclusive evidence.

RACE AS A FACTOR IN CEREBRAL ATHEROSCLEROSIS

Much has been written about the apparent differences in the degree of atherosclerosis among different races and under different climatic conditions. In such studies, it is difficult to separate the influence of climate, diet, and hygiene from those of race. The more careful pathologic studies suggest that the differences among countries, races, and populations are somewhat less significant than suggested by

TABLE 5
RELATION OF WEIGHT TO CEREBRAL ATHEROSCLEROSIS

Age group	*Normal weight*	*%*	*Overweight*	*%*	*Underweight*	*%*
			No atherosclerosis			
0–10	40 : 40	100				
11–20	9 : 9	100			3 : 3	100
21–30	3 : 3	100	2 : 2	100	4 : 4	100
31–40	9 : 11	82	3 : 3	100	5 : 6	82
41–50	14 : 23	61	12 : 17	70	11 : 17	65
51–60	21 : 41	51	14 : 42	33	9 : 27	33
61–70	18 : 57	32	8 : 45	18	13 : 60	22
71–80	6 : 72	8	5 : 41	12	7 : 62	11
81–90	1 : 43	2	0 : 12	0	3 : 43	7
91 –	0 : 1	0	0 : 1	0	1 : 11	9
			Severe atherosclerosis			
0–10	0 : 40	0	0 : 0	0	0 : 0	0
11–20	0 : 9	0	0 : 0	0	0 : 3	0
21–30	0 : 3	0	0 : 2	0	0 : 4	0
31–40	1 : 11	9	0 : 3	0	0 : 6	0
41–50	2 : 23	9	1 : 17	6	2 : 17	12
51–60	7 : 41	17	12 : 42	28	3 : 27	11
61–70	27 : 57	48	23 : 45	51	19 : 60	32
71–80	44 : 72	61	23 : 41	56	45 : 62	72
81–90	34 : 43	79	10 : 12	83	33 : 43	77
91 –	1 : 1	100	1 : 1	100	10 : 11	90

TABLE 6
COMPARISON OF CEREBRAL ARTERIOSCLEROSIS IN AMERICAN AND NORWEGIAN POPULATIONS

Age group	No arteriosclerosis						Moderately severe arteriosclerosis					
	American			Norwegian			American			Norwegian		
	No.	Total	%	No.	Total	%	No.	Total	%	No.	Total	%
0–10	89	89	100	18	18	100	0	89	0	0	18	0
11–20	24	27	89	6	6	100	0	27	0	0	6	0
21–30	26	27	96	6	6	100	0	27	0	0	6	0
31–40	36	45	80	14	15	93	4	45	9	0	15	0
41–50	61	80	76	23	36	64	3	80	4	3	36	8
51–60	80	141	57	38	91	42	20	141	14	16	91	18
61–70	51	143	36	29	144	21	47	143	34	60	144	43
71–80	16	106	15	14	166	8	56	106	51	100	166	59
81–90	2	29	7	4	91	4	23	29	79	70	91	77
91 –	0	3	0	1	12	8	2	3	67	11	12	92

clinical surveys. Studies on degenerative arterial disease implicating the coronary arteries and aorta suggest that there is little difference in the severity of this process in such countries as India, Africa, England, and Egypt.[25–27] In contrast to these reports, there are a number of studies that indicate that atherosclerosis of the coronaries or aorta is conspicuously lower in some races, particularly the more primitive tribes of Africa, Orientals, and Chinese.[28–31]

One of the great difficulties in evaluating the present literature regarding specific etiologic factors in degenerative arterial disease is that various investigators have used different recording and grading technics in their studies. It is imperative that standards be established so that studies done in different parts of the world can be compared.

Using a standard coding system, we carried out a study of the frequency and intensity of cerebral atherosclerosis in 2 groups, 1 in Minnesota and the other in Oslo, Norway. There was a total of 1,175 cases. Table 6 offers a comparative study of these 2 groups by decades. Actually, the 2 groups show strikingly little difference as to frequency and intensity of cerebral atherosclerosis. In the American population, the changes occur somewhat earlier, being present by the second decade. In the Norwegian group, cerebral atherosclerosis does not appear until the fourth decade. However, after the fourth decade, the degree of involvement is almost identical. These groups were not the best for a comparative study, since many of the Americans were of Norwegian birth; thus, it is not surprising that they showed similar changes. More studies of other racial groups will be necessary before conclusive information will be available on the influence of race in cerebral atherosclerosis.

RELATION OF CEREBRAL ATHEROSCLEROSIS TO SOMATIC DISEASE

In order to evaluate properly the influence of somatic factors upon the process of cerebral atherosclerosis, a very extensive study would

TABLE 7
RELATION OF CEREBRAL ATHEROSCLEROSIS TO SOMATIC DISEASE IN 605 CASES OVER 41 YEARS OF AGE

	Normal arteries			Moderate to severe changes		
	Number	Total	%	Number	Total	%
Cardiac disease (exclusive of hypertension)	19	86	22	70	273	25
Kidney disease	2	86	2	5	273	2
Diabetes	2	86	2	12	273	5
Malignant disease	37	86	43	48	273	19
Infectious disease	3	86	4	11	273	4
Others	20	86	23	54	273	20
Cardiovascular accident	3	86	4	58	273	21

be necessary on a large series of cases in which the actual severity and duration of each primary illness could be correlated with the changes in the cerebral vessels. At present, such material is not available to us nor has such a study been carried out. However, as a preliminary survey of such factors, we believed that our study of 605 cases might be of value. Table 7 is a comparative study of somatic disease in subjects with no cerebrovascular changes as compared to those with moderate to severe degenerative changes. For some categories like diabetes, our figures are too small to draw any conclusions. Cardiac disease exclusive of hypertension appears to play no role in the development of cerebrovascular changes. Contrary to the findings of other investigators,[32] chronic infections such as syphilis or tuberculosis seem to play little role in this process. Of significance are our findings in the malignant disease group. Here there seems to be a definite difference. Cerebral atherosclerosis appears to be definitely less severe and less frequent in patients with malignant disease; 2 factors must be considered in these observations—the age of the patients and the possible influence of nutrition. In our studies, we have already pointed out that the factor of body weight does not seem to relate to cerebral atherosclerosis. Moreover, the age grouping of our patients with malignant disease was the same as for those with heart disease and infectious diseases, where no differences were observed. As would be expected, cerebrovascular accidents were much more frequent in the individuals with severe atherosclerosis of the cerebral arteries.

SUMMARY AND CONCLUSIONS

This study is a review of the present status of the significance of exogenous and endogenous factors in cerebral atherosclerosis, based on a study of 1,175 autopsy cases. In all these cases, a uniform, fairly simple coding system was used for the atherosclerotic changes so that these studies can easily be extended or compared by other investigators.

The following conclusions can be drawn:

1. Cerebral atherosclerosis is primarily an intimal change involving the connective tissue elements. Fatty deposits appear to be a secondary process rather than a primary event and may be entirely absent, particularly in the smaller vessels.

2. Of all the factors studied, only 2 seem to play a role in this cerebrovascular degenerative process—hypertension and malignant disease. Patients with hypertension, as indicated by heart weights of more than 450 gm., show a considerable increase in the frequency and severity of this degenerative process, while those with malignant disease showed considerably less. There is a suggestion that diabetes may also hasten the cerebral atherosclerotic process, but our cases were too few to offer any definite conclusions.

3. The frequency and severity of the atherosclerotic process definitely increases with age. However, since this process does occur in many young individuals and is absent in many older subjects, it would appear that it is not due to the aging process itself but is probably the result of some intrinsic changes which act in a chronic fashion and hence would be more prominent in the older age group.

4. Such factors as mechanical stress at points of vessel bifurcation, endocrine disturbances, obesity or malnutrition, chronic infections, and other somatic disease appear to play very little role in cerebral atherosclerosis.

5. Race as a factor in cerebral atherosclerosis is still a moot question. No difference in the frequency and intensity of this process exists between the American and Norwegian population. However, other racial groups will have to be studied with similar technics so that the results can be compared.

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Discussion of "A Study of Etiologic Mechanisms"

W. Jape Taylor, M.D.

THIS PRESENTATION and the previous papers of Dr. Baker are of great interest to all in the field of cardiovascular disease because they deal with the very important aspect of localization of lesions in atherosclerosis, as well as other factors which may shed light on the etiology of this process. It is undeniable that atherosclerosis is a generalized process. The increasing number of patients who have had both their iliac and carotid arteries, as well as points between, either resected or remodeled by the surgeon is strong evidence in support of this concept. From a different viewpoint, however, these patients are just as good evidence that there is sufficient localization of the more severe atherosclerotic lesions to allow surgical approach and correction in a large number of them.

What are the factors that lead to intensification of the generalized process at a given site, and how do the localized lesions progress? Evidence such as that which Dr. Baker has presented raises serious questions with those of us who believe strongly in the lipid theory of atherogenesis because it suggests that the earliest lesions of atherosclerosis are not related to fat deposits. It is of crucial importance to know if the sites in the iliac, femoral, renal, and coronary arteries that show only connective tissue changes in early adult life are the same areas in which lipids are deposited with the formation of typical atherosclerotic plaques. It is unfortunate that the great majority of autopsies still do not provide some of the critical information needed. The internal carotids, the vertebral-basilar system, and the arteries of the extremities are rarely examined in a routine autopsy, and there is remarkably little evidence available on the incidence and localization of atherosclerosis throughout the span of life. Do the fibrous tissue plaques progress and later become lipid-containing atheromatous plaques? Is the atherosclerosis that occurs prematurely in patients with various familial disturbances of lipid metabolism the same as the atherosclerosis that occurs in populations without these genetic disturbances? Why does the experimental atherosclerosis of fat-fed animals not follow the distributional pattern of the human disease? For the purposes of the conference, one would specifically wonder at the usual lack of cerebral atherosclerosis in these animals. Certain clinical evidence suggests that perhaps too many diseases are being lumped under the general designation of atherosclerosis. As an example, one may cite aortic aneurysms and occlusive aortic and iliac disease. The surgical approach to abdominal aneurysms has been one of the major advances in vascular surgery in recent years. Similarly, occlusive disease in the aorta, carotids, or arteries of the extremities can be greatly benefited by proper surgery. Aneurysms and obliterative vascular disease both are considered to be due to advanced arteriosclerosis, and yet it is striking that the two conditions usually do not coexist, although they occasionally may. It would seem possible that these two "arteriosclerotic" manifestations may really be part of different disease entities.

The increased incidence of atherosclerosis with hypertension is well recognized and has been reaffirmed with regard to cerebrovascular disease by Dr. Baker. Turbulence of blood flow at points of bifurcations in the arterial tree has been thought to lead to intimal damage and thus to provide a site for the development of plaques. It is likely that the mechanical factors which may stress the arterial walls are more complex than either hypertension or

turbulence. The hydraulic factors which may lead to the localization of atherosclerotic lesions have been inadequately studied, but two recent observations merit attention. In outlining a theory of the production of cardiovascular murmurs, Bruns[1] has presented evidence which indicates that turbulence is an inadequate producer of acoustic energy in the vascular bed because of the velocities which are involved and has postulated that fluctuating wake formations are more likely to result in murmurs, just as tones were produced by the ancient Aeolian harps. Bruns suggested that such wake-waves might cause vessel damage at sites beyond a bend or bifurcation, and it would seem theoretically possible to predict mathematically where in the abdominal aorta or other arteries these effects would occur. Rodbard[2] has demonstrated that the velocity of flow in a vessel may cause changes in the vessel wall. In his experiments, ligation of a single carotid artery was followed by fragmentation of the internal elastic membrane and the formation of an endothelial "plaque" in the contralateral artery, while subendothelial proliferation developed in the ligated vessel. These effects were presumed to be the result of variations in velocity of blood flow and consequent drag on the boundary layer between blood and lining. Investigation of such hydraulic theories which may influence the localization of intimal damage and the progression of atherosclerosis is definitely needed.

The final consideration, and perhaps the most crucial of all, is the fact that no dependable method for the in vivo study of human atherosclerosis is available. The number of myocardial infarctions or strokes that an arteriosclerotic patient has on a regimen of fat restriction or anticoagulation is, at best, very indirect evidence regarding the rate of progression of atherosclerosis in the patient. The rate of fall and rise in the serum cholesterol or other lipid fractions may not be correlated in any way with the changes in the arterial walls, although animal experimentation would suggest that it is. Angiograms are of great clinical usefulness but allow only the most gross index of the progression of disease. Similar objections can be raised to almost all of the methods which we use. One of the major challenges in the study of atherosclerosis is the development of a technic which will permit the evaluation of the multiple factors which determine the "natural" behavior of atherosclerosis and the effects of our various therapeutic regimens.

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Aspects of cerebral circulatory physiology of relevance to cerebrovascular disease

Louis Sokoloff, M.D.

MANY OF THE CLINICAL SYNDROMES of cerebral circulatory disease are manifestations of cerebrovascular insufficiency. By "vascular insufficiency" is meant the inadequacy of the circulation to provide the tissue with the blood flow required to support its metabolic activities in all its physiologic states. It may be present continuously or occur intermittently whenever blood flow falls below normal levels, or it may become manifest only under conditions of increased metabolic demand, when the blood flow cannot be increased to the levels required by the additional load.

Several special features of cerebral function and metabolism tend to predispose the brain to the developement of vascular insufficiency. Cerebral functional activity requires a great deal of chemical energy, and relatively large amounts of oxygen must be utilized to provide this energy.[1] For example, the brain, which comprises only about 2% of total adult body weight, alone accounts for almost 20% of the total basal body oxygen consumption. In normal man, this high metabolic rate appears to be continuously sustained without any appreciable change, even during periods of sleep[2] or mental exercise.[3] It is only in pathologic states that the cerebral metabolic rate has been found to be decreased.[1,4,5] Furthermore, a continuously high rate of oxygen consumption is essential for uninterrupted cerebral functional activity. Cerebral function is dependent on an obligatory oxidative carbohydrate metabolism; unlike many other tissues as, for example, skeletal muscle, the brain cannot maintain its structural and functional integrity even for a short time in the absence of oxygen and glucose.[1] These substances, particularly the former, are stored in the brain in such small amounts compared to their rates of utilization that they must be continuously replenished by the circulation. Thus, for example, if cerebral blood flow is completely interrupted, consciousness is lost within ten seconds,[6] or about the time required for the oxygen normally present in the blood contained within the brain to be consumed.[4] It is not only cerebral functional activity, however, which is so exquisitely sensitive to oxygen lack, for, if its blood flow is restricted for only a few minutes, irreversible structural damage to the brain ensues.[7]

In summary, the following characteristics render the brain completely dependent on a continuously uninterrupted blood supply: [1] an almost constant high rate of oxygen and glucose consumption; [2] functional activity which depends on an obligatory oxidative carbohydrate metabolism and cannot be supported even momentarily by anerobic metabolism; [3] relatively low storage capacity for oxygen and glucose, the essential substrates of its metabolism; [4] the rapid development of permanent structural damage in the absence of adequate amounts of oxygen and carbohydrate. It is for these reasons that the brain is so sensitive to any impairment of its blood supply and prone to develop the signs and symptoms of vascular insufficiency. Fortunately, the mechanisms normally regulating the cerebral circulation are particularly well adapted to the special requirements of the brain, and it would probably be helpful to consider briefly at this point the factors which determine and regulate the cerebral blood flow. This subject has been comprehensively covered in recent reviews.[5,8]

REGULATION OF THE CEREBRAL CIRCULATION

As in all vascular beds, the blood flow to the brain is dependent upon 2 opposing variables:

[1] the blood pressure gradient across the vascular bed which provides the driving force maintaining the blood flow through the tissues; and [2] the cerebrovascular resistance which is comprised of all the factors which serve to impede the flow of blood through the vascular bed.

Blood pressure gradient. The cerebral blood pressure gradient is equal to the difference between the arterial pressure at the head level and the cerebral venous pressure. Since cerebral venous pressure is usually small compared to arterial blood pressure, it generally exerts only negligible effects on the pressure gradient and cerebral blood flow. It may be important under conditions of accelerative stress, where it serves to balance the hydrostatic effects on the arterial pressure head.[9] Also, in the presence of cerebrovascular disease, when cerebral blood flow may already be marginal, abrupt rises in venous pressure during straining or Valsalva-like maneuvers may precipitate symptoms of cerebrovascular insufficiency, particularly if it is also associated with a simultaneous fall in arterial blood pressure.

The arterial blood pressure at the head level is normally zealously guarded by intrinsic circulatory reflexes of the carotid sinus type, which do not appear to affect directly the tone or caliber of the cerebral vessels. Such mechanisms tend to maintain the cerebral blood pressure gradient constant without altering cerebrovascular resistance and thus help to maintain a relative constancy of the cerebral blood flow. When the capacity of these mechanisms is exceeded and arterial blood pressure is altered, adjustments in the tone of the cerebral vessels occur which tend to counteract the effects of the arterial pressure change. In normal subjects, these adjustments are sufficient to maintain a relatively constant cerebral blood flow in the face of fairly wide changes in arterial blood pressure.[5] Ultimately, however, when the mean arterial blood pressure falls to a critical value somewhere between 50 and 70 mm. Hg, cerebral blood flow tends to fall and signs and symptoms of cerebrovascular insufficiency may appear;[5] when the mean arterial blood pressure falls below 35 mm. Hg, cerebral blood flow falls to levels inadequate to maintain consciousness.[10] With certain types of vascular disease, such as malignant hypertension, adjustment of cerebrovascular tone appears to be more limited and symptoms of cerebrovascular insufficiency occur with proportionately lesser declines in blood pressure.[10] In atherosclerotic patients with chronically low cerebral blood flow, there are wide variations and no consistent pattern in the relationships among blood pressure reduction, blood flow decline, and clinical symptoms. This suggests individual differences in the distribution of the total cerebral blood flow and the areas of brain most involved.[11]

Cerebrovascular resistance. Over a wide range of arterial blood pressure, the cerebral circulation is regulated by the factors which govern the resistance to the flow of blood through the cerebral vessels. Cerebrovascular resistance, which is estimated by the ratio of cerebral blood pressure gradient to cerebral blood flow, is the net effect of a number of factors.

Blood viscosity. The viscosity of blood varies chiefly with red cell concentration. Consequently, with anemia, cerebrovascular resistance is decreased and cerebral blood flow increased.[12,13] With polycythemia, opposite effects occur; indeed, some of the lowest rates of cerebral blood flow in conscious man have been recorded in this condition.[4] This observation perhaps has some relationship to the prevalence of cerebrovascular accidents in these patients. With hypothermia, marked increases in blood viscosity and cerebrovascular resistance have been described.[14]

Intracranial pressure. The thin-walled cerebral vessels have exerted upon them the pressure of the cerebrospinal fluid within the rigid cranial cavity. This pressure raises the frictional resistance to the flow of blood through them. Increased intracranial pressure is, therefore, associated with increased cerebrovascular resistance and, if high enough, can reduce cerebral blood flow to a point incompatible with consciousness.[4] That other factors may be involved, however, is suggested by the finding that reduction in the increased intracranial pressure in such cases fails to restore a normal cerebral blood flow.[15]

Size and tone of cerebral vessels. The major source of the cerebrovascular resistance resides in the frictional resistance to blood flow in the cerebral vessels themselves, and this in turn

is markedly influenced by the diameters of the vessels. When the cerebral vessels are narrowed by vascular disease such as arteriosclerosis, cerebrovascular resistance is increased and cerebral blood flow reduced.[5,16,17] Within the limits imposed upon them by their morphologic state, the cerebral vessels are capable of altering their size and tone, thus providing the means for the dynamic regulation of the cerebral blood flow in accordance with the changing needs of the brain.

In contradistinction to most other vascular beds, *nervous control* of cerebrovascular tone, if at all existent, is yet to be demonstrated. This is despite clear anatomic evidence of sympathetic and parasympathetic innervations of the cerebral vessels and observations of cerebrovascular responses to interruption or stimulation of these nervous pathways in animals under laboratory conditions.[8] No evidence has been obtained in man to indicate any major nervous effects on the cerebral vessels. Procaine block of the stellate ganglion performed bilaterally in normotensive and hypertensive patients[18] and unilaterally in patients with chronic cerebrovascular disease or acute cerebrovascular accidents[19] does not alter cerebrovascular resistance or blood flow. Shenkin, Cabieses, and van den Noordt[20] found reduced cerebrovascular resistance after bilateral stellate ganglionectomy, but these results were complicated by the development of anemia in the interval between the control and postoperative measurements. The role of the nerve supply to the cerebral vasculature therefore remains to be determined. It is conceivable that it is involved in local reflexes regulating the distribution of the total blood flow among the component brain tissues.

Regulation of cerebrovascular tone appears to be accomplished chiefly by *chemical factors*. It has been repeatedly demonstrated in animals and man that the respiratory gases exert greater influence on cerebrovascular resistance and blood flow than any other agents or means of physiologic significance. Increased blood CO_2 tension, produced by inhalation of 5 to 7% CO_2, increases cerebral blood flow by approximately 75%,[21] chiefly by dilation of the cerebral vessels. The cerebral vessels can respond to increases in arterial pCO_2 as low as 4.5 mm. Hg, the change produced by the inhalation of about 3% CO_2.[22] Reduced blood pCO_2 produced by hyperventilation results in cerebral vasoconstriction and a decrease in cerebral blood flow.[21] Somewhat less effective, but still quite marked, are the effects of alterations in blood oxygen tension. A fall in blood oxygen tension dilates cerebral vessels and increases cerebral blood flow, and increased blood oxygen tension has the opposite effects.[21] The latter action may be indirect and secondary to the hyperpnea and hypocapnia frequently associated with the breathing of high-oxygen gas mixtures.[23] Heyman and his associates[17] have found that the breathing of 85 to 100% oxygen in elderly subjects with cerebrovascular disease causes an increase in cerebrovascular resistance and a decrease in cerebral blood flow which, although less than observed in normal subjects,[21] are still sufficient to constitute a hazard in patients with acute cerebrovascular accidents. They recommend instead the use of 50% oxygen, which has negligible effects on cerebral blood flow.

Acids and bases have been reported to cause cerebral vasodilation and vasoconstriction, respectively, but these effects have been neither profound nor consistent.[8] In fact, opposite effects have also been observed,[8,24] although it is likely that in these cases other factors such as secondary changes in blood pCO_2 obscured any direct effects of *p*H on the cerebral circulation.

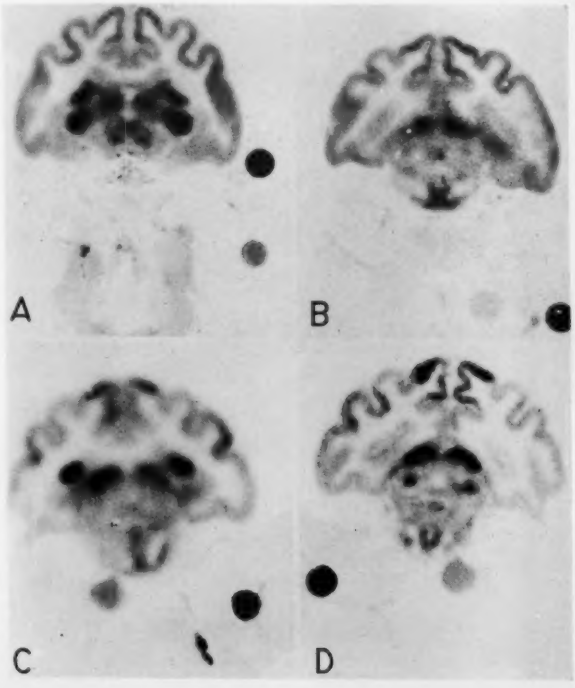
The facts that increased carbon dioxide tension and reduced oxygen tension, the changes to be expected in the tissues when their metabolic rate is increased, cause cerebral vasodilation, and that opposite alterations in the gas tensions cause constriction have led to the popular hypothesis that cerebral blood flow is adjusted to the metabolic activity of the brain through the mechanism of chemical regulation of cerebrovascular tone by the products of tissue metabolism. Since metabolic activity is probably related to functional activity, a mechanism would then be available whereby cerebral blood flow is regulated by the functional activity of the brain.

THE CEREBRAL CIRCULATION IN CEREBROVASCULAR DISEASE

Considerable quantitative information has been acquired in recent years by studies of

the cerebral circulation in various types of cerebrovascular disease. With cerebral hemangiomas with arteriovenous shunts, cerebrovascular resistance is drastically reduced and cerebral blood flow tremendously increased;[25,26] marked differences in blood flow between the two sides may occur, with a preponderance of flow on the affected side.[26] Unilateral carotid occlusion has been found to produce no significant effects on cerebral blood flow in patients who do not have signs and symptoms of hemiparesis;[27] in those who do, cerebral blood flow falls, and evidence has been obtained to implicate a high vascular resistance in the circle of Willis as the responsible factor.[27] With cerebral arteriosclerosis, cerebrovascular resistance is increased and cerebral blood flow reduced regardless of whether an apoplectic attack has occurred;[5,16,17,19] with acute apoplexy, cerebral oxygen consumption may be profoundly depressed if coma is present.[5] These abnormalities are not altered by stellate ganglion block.[5,19] Both cerebral blood flow and metabolic rate have been found to decline with advancing age.[28] The results of recent studies suggest that these changes are not caused by chronologic aging per se but rather by arteriosclerosis, which leads first to a reduction in cerebral blood flow and a relative cerebral anoxia and, finally, after a prolonged period of time of the latter condition, to a fall in cerebral oxygen consumption.[29]

This rather impressive mass of knowledge about the human cerebral circulation has been acquired almost entirely by means of the nitrous oxide method of Kety and Schmidt[30] and its Scheinberg[31] and Lassen modifications.[32,33] Despite their great value as research tools, however, these technics have not proved to be clinically useful as diagnostic or prognostic procedures, except, perhaps, in the case of arteriovenous anomalies of the brain.[25,26] It is not the fault of the methods, however;



Autoradiographs illustrating effects on local cerebral blood flow in unanesthetized cat of retinal stimulation with photoflash for five minutes. In general, density reflects blood flow rate, and areas of greater density represent areas with higher blood flow rate. Circular areas of uniform density are autoradiographic representations of gelatin standards containing known amounts of radioactivity added for calibration purposes. [A] Control experiment in cat which was blindfolded. Note striate cortex and lateral and medial geniculate ganglia. [B] Autoradiograph from different brain section of same cat. Note striate cortex and superior colliculi. [C] Autoradiograph from brain of cat after retinal stimulation by photoflash for five minutes. Note marked increase in density in discrete areas of striate cortex and also relative increase in density in lateral as compared with medial geniculate ganglia. [D] Autoradiograph from different brain section of stimulated cat. Note darkened areas in striate cortex and superior colliculi. (From Sokoloff[30])

LOCAL CEREBRAL BLOOD FLOW IN THE CAT

Structure	*Blood flow (cc. per gm. per minute) (Mean ± standard error)*	
	Conscious (10 cats)	*Light thiopental anesthesia (11 cats)*
I. Superficial cerebral structures		
Cortex		
Sensory-motor	1.38 ± 0.12	0.65 ± 0.07*
Auditory	1.30 ± 0.05	0.72 ± 0.07*
Visual	1.25 ± 0.06	0.77 ± 0.09*
Miscellaneous-association	0.88 ± 0.04	0.67 ± 0.06*
Olfactory	0.77 ± 0.06	0.62 ± 0.07
White matter	0.23 ± 0.02	0.26 ± 0.04
II. Deep cerebral structures		
Medial geniculate ganglion	1.22 ± 0.04	0.81 ± 0.09*
Lateral geniculate ganglion	1.21 ± 0.08	0.79 ± 0.07*
Caudate nucleus	1.10 ± 0.08	0.91 ± 0.11
Thalamus	1.03 ± 0.05	0.71 ± 0.09*
Hypothalamus	0.84 ± 0.05	0.55 ± 0.06*
Basal ganglia and amygdala	0.75 ± 0.03	0.58 ± 0.05*
Hippocampus	0.61 ± 0.03	0.59 ± 0.04
Optic tract	0.27 ± 0.02	0.22 ± 0.08
III. Midbrain and pons		
Inferior colliculus	1.80 ± 0.11	1.41 ± 0.14*
Superior olive	1.17 ± 0.13	1.56 ± 0.27
Superior colliculus	1.15 ± 0.07	0.82 ± 0.10*
Pontine gray	0.88 ± 0.04	0.61 ± 0.03*
Reticular formation	0.59 ± 0.05	0.49 ± 0.06
Pontine white	0.24 ± 0.02	0.31 ± 0.04
IV. Cerebellum, medulla, and spinal cord		
Cerebellum		
Nuclei	0.79 ± 0.05	0.56 ± 0.08*
Cortex	0.69 ± 0.04	0.57 ± 0.05*
White matter	0.24 ± 0.01	0.29 ± 0.06
Medulla		
Vestibular nuclei	0.91 ± 0.04	0.84 ± 0.10
Cochlear nuclei	0.87 ± 0.07	0.99 ± 0.14
Pyramids	0.26 ± 0.02	0.28 ± 0.03
Spinal cord		
Gray matter	0.63 ± 0.04	0.53 ± 0.07
White matter	0.14 ± 0.02	0.15 ± 0.06

*Statistically significantly different from conscious control values ($p < 0.05$)

they achieve all they were designed to do with a reasonable degree of accuracy. Dr. Lassen, whose bilateral krypton-85 modification[33] has improved the precision of the technic, may have more to say about this matter in the subsequent discussion. The problem is that there is no sharp dividing line between normal and abnormal values for cerebral blood flow. Patients with clinically obvious cerebrovascular insufficiency may have values as high as those of normal subjects and vice versa. When the cerebral blood flow value is distinctly below normal limits, the clinical picture is usually sufficiently obvious without subjecting the patient to such a formidable procedure.

A number of reasons exist for the overlapping of cerebral blood flow values between normal subjects and patients with cerebrovascular disease. Least important of all is the fact that the nitrous oxide method measures the blood flow of an average fraction of the total perfused cerebral tissues taken as a whole rather than the total blood flow of the brain. If there is a completely unperfused area, as might occur in the case of an infarction, this would not be reflected in the blood flow value obtained with the nitrous oxide technic. In such cases, a method for measuring total blood flow might be more sensitive, but then the brain size would become a relevant variable which would require estimation.

More important problems are the timing of the measurement and the conditions under which it is made. Because of the brain's extreme sensitivity to impairment of its blood supply, clinical symptoms and even brain damage may occur during a brief decline in cerebral blood flow which may have returned to normal by the time of its measurement. Similarly, in patients with cerebrovascular disease, increases in metabolic demand may fail to be accompanied by commensurate increases in blood flow; clinical signs and symptoms may then appear because of a relative cerebral ischemia which may not be recognized or may not even be present at the time and under the conditions of the cerebral blood flow measurement. It is a situation analogous to the findings of a normal basal cardiac output in congestive heart failure or a normal peripheral blood flow in resting patients with peripheral vascular disease. That increased demand for blood flow may be stimulated in the brain is demonstrated by the autoradiographs in the figure; these illustrate the effectiveness of photic stimulation of the retina in increasing blood flow in the visual cortex, lateral geniculate ganglia, and superior colliculi of the conscious cat's brain.[34] Furthermore, the mechanism of the circulatory response appears to be chemical, for it is a delayed response which was observed after five minutes and not after only one minute of continued stimulation. Patients with cerebrovascular disease have a cerebrovascular reactivity to the chemical factors, oxygen and carbon dioxide, that is normal percentagewise but reduced on an absolute basis.[5,17,35] Since the demands of increased functional activity may require an absolute rather than a percentagewise increase in blood flow, it is conceivable that this defect may predispose such patients to the development of relative cerebral ischemia.

The major limitation of cerebral blood flow studies in cerebrovascular disease is the problem of localization. As previously pointed out, currently available methods for human studies measure blood flow of the brain as a whole. However, the effects of cerebrovascular disease are usually manifested in localized areas, and changes in blood flow in these areas may not be reflected in the value obtained for the brain as a whole. In fact, although the autoradiographs in the figure clearly show evidence of increased blood flow in the visual cortex during retinal stimulation, the areas affected are so small and discrete that, when total average visual cortical blood flow is calculated, the effect is obscured and no significant difference is observed.[34]

The brain is composed of many structures with almost as many different rates of blood flow. In the table are presented the blood flow values in 28 structures of the cat brain in conscious and anesthetized states.[36,37] The fact that only 14 structures showed significant changes in blood flow under anesthesia and the remarkable discreteness of the effects of retinal stimulation seen in the figure indicate that blood flow in the component structures of the brain may vary independently. Conclusions about one cannot be drawn from observations of the others or, indeed, from observations of the brain as whole. These data were obtained

by the radioactive inert gas technic of Kety and his associates.[36–38] Unfortunately, this technic is applicable only to animals, but, if and when a method is developed which permits similar measurement of local blood flow in the human brain, it is certain to be of immense usefulness in the study of cerebrovascular disease.

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Studies of internal jugular blood in cerebrovascular disease

Niels A. Lassen, M.D.

As a supplement to Dr. Sokoloff's review, I intend to discuss in somewhat more detail results obtained by applying the inert gas method of Kety and Schmidt[1] to the study of patients with cerebrovascular disease.

Arteriovenous anomalies of the cerebral vessels are associated with gross abnormalities of internal jugular blood.[2–7] The figure shows the inert gas saturation curves obtained in a patient with a large arteriovenous angioma over the right hemisphere.[7] Radioactive krypton was used as inert gas. The curves to the left were obtained before neurosurgical intervention. The upper curve gives the krypton concentration in the femoral artery during fourteen minutes of krypton inhalation. The middle curve is the abnormal one, and the abnormal feature is its close resemblance to the arterial upper curve. This middle curve is from the right internal jugular vein, that is, from the same side as the angioma.

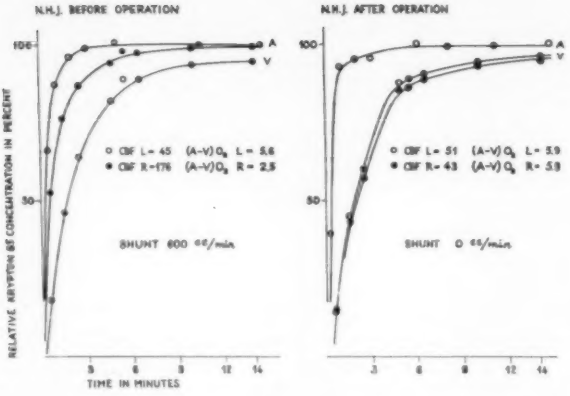
Here, the calculated perfusion rate was 4 times the normal rate. The oxygen saturation of the blood was also abnormally high. On the contralateral side, showed by the lower curve, normal values were found. The right-hand side of the figure gives the results obtained in a bilateral study performed after the arteriovenous anomaly had been removed surgically. Normal values were now found on both sides, demonstrating the essential completeness of the operative extirpation in this case. We estimated that the shunt flow had been reduced from 600 cc. per minute to zero.

This case illustrates the use of the inert gas method, showing that very gross local abnormalities may, after all, give rise to measurable changes in internal jugular blood. It is not intended, however, to suggest that such studies should be used clinically in cases of arteriovenous anomalies. Neurologic evaluation and arteriography give adequate information, to which the addition of quantitative data is of no obvious value.

The stroke syndrome was studied in the acute phase by Lindén[8] using Scheinberg's modification of the inert gas method.[9] Subnormal values for blood flow and oxygen uptake were found in confused or comatose patients with apoplexy. Despite the fact that *focal* vascular insufficiency initiates the cerebral catastrophe, no evidence of *diffuse* cerebrovascular insufficiency was found, since no reduction of the oxygen saturation of cerebral venous blood was noted.

This is not so surprising. The focal lesion is presumably quite small compared to the size of the whole brain; moreover, slow perfusion or no perfusion through the focus reduces or prevents entirely any direct reflection of the local circulatory or metabolic derangement in the internal jugular blood. What is observed regards mainly the malfunction of the remainder of the brain. Here, evidently, a diffusely abnormal functional state prevails in patients who are comatose because of a stroke, but the diffuse derangement is seemingly not caused by a reduced oxygen supply. This conclusion is consonant with the well known lack of striking effect of oxygen or carbon dioxide therapy in comatose apoplectic patients. That a circumscribed and relatively small cerebral infarction may produce a diffuse depression of cerebral function is presumably related to the integrated functional organization of the brain.

Acute hypertensive encephalopathy is associated with a reduction of cerebral oxygen uptake.[10,11] Whether due to essential hyper-


N.H.J. BEFORE OPERATION
N.H.J. AFTER OPERATION
RELATIVE KRYPTON 85 CONCENTRATION IN PERCENT
TIME IN MINUTES
A
V
CBF L = 45 (A-V)O2 L = 5.6
CBF R = 176 (A-V)O2 R = 2.5
SHUNT 600 cc/min
CBF L = 51 (A-V)O2 L = 5.9
CBF R = 43 (A-V)O2 R = 5.9
SHUNT 0 cc/min

Inert gas saturation curves before and after operation in a patient with a right-sided intracranial arteriovenous aneurysm.[7] The cerebral blood flow (CBF) in cubic centimeters per 100 gm. per minute, the cerebral arteriovenous difference for oxygen, $(A\text{-}V)O_2$, in cubic centimeters of O_2 per 100 cc. of blood (vol%), and the volume of blood passing the shunt in cubic centimeters per minute are indicated.

tension or hypertensive toxemia of pregnancy, the over-all cerebral perfusion is not reduced. Thus, the cerebral symptoms cannot be due to generalized cerebrovascular insufficiency. Animal studies suggest strongly that multiple *focal* angiospasms leading to areas of hypoxia and functional disturbance are the pathophysiologic mechanism of the acute hypertensive encephalopathic attack.[12] This is not incompatible with the finding of a normal cerebral perfusion in patients with hypertensive crisis, since it must be stressed here again that the methods of study are unable to detect such focal dysfunctions. Presumably, the areas of ischemia are quite small and, therefore, contribute little to over-all perfusion rate; if the blood flow is sufficiently slow, their contribution is further minimized.

Atheromatosis of the cerebral arteries is undoubtedly of great importance for the development of acute focal cerebrovascular disease. Because cerebral atheromatosis increases with age, it has been thought that it is the cause of the senile brain disorders. This concept, that senility is due to inadequate plumbing, is not well founded. But it is certainly well accepted. At the Conference on Cerebral Vascular Disease held in January 1954 in Princeton, N. J., Dr. D. P. Barr aptly summarized this problem by stating: "It is believed, without conclusive proof, that arteriosclerosis, through production of chronic ischemia is responsible for the widespread degeneration of nerve cells and nerve tracts which accompany the mental deterioration and dementia in old people."[13]

Inert gas studies in senile brain disorders have been my main field of interest for the past several years. The method used was the krypton-85 modification of the inert gas method, and experimental errors were kept quite low by increasing the number of blood samples and employing bilateral jugular punctures.[14,15] A fairly close correlation between mental deterioration and decrease in cerebral oxygen uptake was found.[16–18] However, much to our surprise, we were unable to find physiologic evidence of cerebrovascular insufficiency in the mentally deteriorated patients. Their cerebral blood flow was subnormal, but it was only reduced in proportion to the reduction in oxygen uptake. Thus, the cerebral venous oxygen saturation was normal (average, 56%), and, after carbon dioxide inhalation, it increased to an average of 77%, as compared to 74% in the normal controls.[16] Therefore, a normal degree of vasodilation occurred in the senile patients. Similar results have also been obtained by other investigators (see the more detailed discussion in Lassen[19,20]).

You will understand that my conclusion is quite the opposite of that expressed by Dr. Sokoloff, who felt that arteriosclerosis "leads to a reduction in cerebral blood flow and a relative cerebral anoxia and, finally, after a prolonged period of the latter, to a fall in cerebral oxygen consumption." My belief is that parenchymatous degeneration is the pri-

mary event. Concomitant changes are a reduction in oxygen uptake and blood flow. Cerebral atheromatosis and anoxia play no role in this diffuse and slowly progressing process.

Actually, I do not believe that present experimental evidence permits a really well-founded opinion about this intriguing question regarding the role of tissue hypoxia in diffuse brain degeneration of old age, since one cannot make reliable deductions regarding tissue oxygen tensions in the various parts of the brain from observations of the oxygen content of internal jugular blood. Since Dr. Sokoloff holds the same opinion on the limitations inherent in studies of internal jugular blood, I am afraid that we must disappoint the audience by refraining from giving you the thrill of having us enter a heated argument over the relative virtues of our opposite points of view.

Dr. Sokoloff ended his presentation by suggesting the usefulness of a local blood flow technic applicable to man. I should like, in ending my comments, to add that even more needed is information regarding local tissue oxygen tensions, reflecting adequacy of circulation. The necessity of exposing the brain by craniotomy imposes a definite limitation for such studies.

Despite this difficulty, the clinical application of experimental technics for measuring perfusion[21] and tissue oxygen tension inside the brain or on its exposed surface is likely to yield very valuable information. It appears to be the best approach to solve the riddle of cerebrovascular disease in old age. Therefore, it is with anticipation that I look forward to the last section of this afternoon's session, where such local technics will be discussed.

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Discussion of "Aspects of Cerebral Circulatory Physiology of Relevance to Cerebrovascular Disease"

Peritz Scheinberg, M.D.

Dr. Sokoloff has succinctly delineated the major liabilities of the nitrous oxide technic for measuring cerebral blood flow and the limitations of the data derived from this method. The technic does not provide information pertaining to local or regional changes in cerebral blood flow, and the time required for the measurement (ten minutes) does not permit evaluation of rapid changes in cerebral circulation. However, the original technic, together with various modifications based upon it, remains the only proved method of quantitatively assaying the physiology of the human cerebral circulation. The limitations heretofore mentioned should not vitiate the value of the large body of facts accumulated by it.

It is frequently difficult to explain clinical phenomena by physiologic data, though we are often tempted to do so. However, measurements of cerebral circulatory and metabolic functions have shed considerable light on the pathogenesis of various types of cerebrovascular disease. Such studies have indicated, for example, that the development of cerebral ischemia and even infarction after reduction in effective cerebral arterial pressure is a likely consequence of the reduction in cerebral blood flow that arterial hypotension induces. The compensating mechanism of increased oxygen and glucose extraction by the brain as cerebral circulation slows eventually fails and cerebral oxygen and glucose metabolism decrease. This decrease is frequently though not invariably accompanied by clinical symptoms of cerebral ischemia.

Although the syncope which occurs with postural hypotension is rarely associated with enough focal neurologic change to suggest brain infarction, its mechanism can probably be explained by the rapid and striking reduction in cerebral blood flow and metabolism noted in these individuals. The pooling of blood in hypotensive dependent vessels results in a rapid fall in cardiac output and arterial pressure and consequent decrease in cerebral blood flow.

It is well known that hypertension is accompanied by an increased incidence of cerebrovascular disease. The increase in thrombotic vascular disease with hypertension can probably be explained by an increased incidence of cerebral atherosclerosis and arteriosclerosis. Cerebral metabolic studies have not explained the mechanism of hypertensive cerebral hemorrhage, although such studies have revealed the existence of intense cerebral vasoconstriction and strikingly elevated cerebrovascular resistance. How this vasoconstriction may eventually result in arterial rupture and apoplexy is not known. Studies have indicated that the increased cerebrovascular tonus is invariably diminished in conjunction with reduction of the arterial pressure.

The etiologic importance of atherosclerosis in the production of cerebrovascular thrombosis and infarction is well established clinically, although cerebral physiologic studies have not entirely clarified this relationship. Available studies indicate that patients with clinical cerebrovascular disease, with or without current neurologic changes, do not show alterations in cerebral circulatory and metabolic functions beyond those attributable to the normal aging process. If cerebrovascular

disease is accompanied by alterations in mental status, there is a significant reduction in cerebral blood flow and cerebral oxygen and glucose metabolism, but this may be nothing more than an indication of the severity of the vascular disease. The common clinical denominator for the magnitude of depression of brain blood flow and metabolism is the severity and not the type of the disease process. As yet, laboratory studies have shown no specific distinction between the metabolic alterations which occur with the presenile and senile dementias and those of advanced cerebral arteriosclerosis, despite the obvious clinical and pathologic differences between them. Indeed, there is not yet a specific correlation between the degree of disturbance of cerebral oxygen or glucose consumption and the extent of intellectual dysfunction due to any disease process. In this regard, it is of interest that studies made on 4 patients who manifested the clinical picture of akinetic mutism due to mesencephalic infarction revealed no significant alteration in cerebral blood flow and oxygen and glucose metabolism. This is an example of a small lesion producing a major alteration in the patient's state of consciousness and again illustrates the inability of the inert gas technic to measure the effects of local changes in blood flow and metabolism, except as these changes influence total cerebral blood flow and metabolism.

The treatment of cerebrovascular disease, with the possible exception of the use of anticoagulant medication, has continued to be empiric. Although the effectiveness of any given therapy must be evaluated clinically rather than physiologically, cerebral metabolic studies have elucidated the physiologic effects of certain types of treatments used for acute and chronic cerebrovascular disease. The objective of therapy in occlusive cerebrovascular disease remains somewhat obscure. Most advocated treatments have had the objective of producing dilation of cerebral vessels, improvement in cerebral blood flow, and consequent alleviation of symptoms. Adequate evidence exists that the local cerebral hypoxia caused by vascular thrombosis and the accumulation of acid metabolites locally in the infarcted tissue probably results in maximal local cerebral vasodilation. Furthermore, many of the treatments used for this purpose are ineffective clinically and do not produce cerebral vasodilation. This includes stellate ganglion block, nicotinic acid, aminophylline, and oxygen by inhalation. Indeed, the last two are known to produce cerebral vasoconstriction. The one commonly used, effective cerebral vasodilator is CO_2 in concentrations from 2½ to 10%. Available clinical studies indicate that even this potent agent is ineffective in reversing the symptoms of cerebral infarction.

Recently, hypothermia has been utilized to protect the brain from the hypoxia induced by cardiac surgery or temporary ligation of the cephalic vessels during neurosurgical procedures. The reduction in cerebral oxygen consumption and the secondary decrease in cerebral blood flow which occur with hypothermia offer a rational explanation for the mechanism of this protection as well as for the concomitant reduction in brain volume.

Despite the limitations of the method, the nitrous oxide technic has provided the type of physiologic information which permits the clinician to think more intelligently about the problems of cerebrovascular disease.

Interaction of cerebral hemodynamics and metabolism

John S. Meyer, M.D., and Fumio Gotoh, M.D.

THE PURPOSE of this communication is to summarize experimental evidence showing that changes in cerebral metabolism influence local blood flow and, conversely, that cerebral metabolism may become temporarily or permanently reduced when local circulation fails. An attempt will be made to define the regulatory and biochemical mechanism within the brain whereby increased local metabolism results in localized hyperemia sufficient to meet the increased metabolic demand. New experimental data will be presented which support the principle that the more active the local metabolism, the greater the local cerebral blood flow. Finally, evidence will be presented showing that, after cerebrovascular occlusion, the same regulatory mechanism tends to increase collateral blood flow.

Previously, hemodynamic changes in the pial vessels have been observed and described after experimental cerebrovascular occlusion.[1–3] In brief, if a good collateral circulation was present (via the circle of Willis or the pial arterial anastomoses) after occlusion of a cerebral vessel, rapid circulation was maintained and there was no change in cortical function. If collateral circulation failed, the flow of blood in the pial vessels slowed, with regional cyanosis of the terminal vascular net. Normal axial flow of the blood elements was lost, and turbulent flow often resulted. Such turbulent and slowed flow resulted in tissue anoxia with more frequent collision of erythrocytes, which tended to aggregate. Tissue anoxia resulted in endothelial damage, loss of plasma fluid, and localized hemoconcentration with hyperproteinemia. Presumably, this produced a change of electrostatic charge on the surface of the erythrocytes, resulting in their aggregation into segments and their slow movement in small vessels. As a result of these localized changes in the properties of the blood, there was increased viscosity and further slowing of flow and stasis might result. If sluggish flow persisted, anoxic *but reversible* paralysis of neuronal function occurred, recovery being possible whenever local blood flow was restored. If local tissue oxygen persisted below 20% of normal (0 to 4 mm. Hg), irreversible infarction resulted.

Observations reported in the present communication have been made using new recording technics which we have developed for correlating localized changes in cerebral metabolism with changes in cortical blood flow. Quantitative measurements of cortical *p*H, pCO_2, and pO_2 in different areas of the brain were continually recorded with concurrent changes in local blood flow and electroencephalographic activity. In addition, the concentration of alveolar CO_2 and the systemic blood pressure were also recorded.

MATERIAL AND METHODS

Observations have been made in 30 monkeys (Macacus rhesus) and 13 cats using ether and regional Xylocaine anesthesia and immobilization with d-tubocurarine. All operative exposures were performed under ether anesthesia. Since certain experiments such as photic stimulation and the induction of seizures required the alert state, records were made after careful regional anesthesia of all operative fields to avoid pain. Tracheostomy was routinely performed, and the alveolar CO_2 concentration was maintained constant (around 4%) with a Harvard variable speed respirator pump. A craniectomy was performed, but the dura was left in place and the electrodes were inserted through small holes cut in the dura

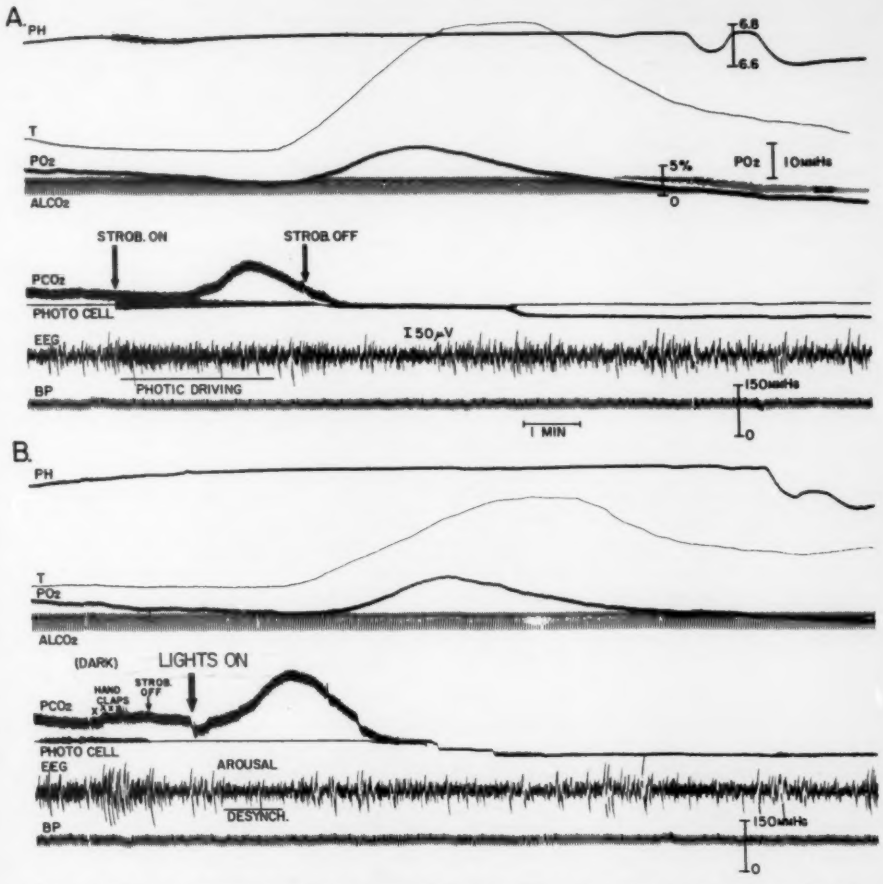

Fig. 1. A and B are strips of a continuous record made in a monkey immobilized with d-tubocurarine and local anesthesia. Recordings of electroencephalogram, pH, pO_2, pCO_2, and cortical blood flow (T) were made from occipital lobe (visual cortex). Alveolar CO_2 ($ALCO_2$) and femoral blood pressure were continuously recorded. Stroboscopic stimulation is indicated by photocell record. Initial pO_2 levels are estimated at 15 mm. Hg. Calibration of pH, pO_2, blood pressure, electroencephalogram, and time are shown in A. Initial pCO_2 levels are estimated at 64 mm. Hg, but exact calibration of pCO_2 is not known since amplifiers were changed after calibration. In both records, after activation, the pCO_2 levels fell after rising and were mechanically limited by photocell pen. [A] Effects of stroboscopic stimulation with photic driving appearing in the electroencephalogram. Brain tissue pO_2 falls, and brain pCO_2 rises, followed after sixty to ninety seconds by localized increase of cortical blood flow and increase in cortical pO_2 and late fluctuation in pH. Similar response was not seen in Sylvian region with photic stimulation. [B] Minimal change with hand claps and brief photic stimulation at faster speed; arousal response resulted when lights were turned on. Arousal reaction is accompanied by desynchronization of electroencephalogram, decrease in cortical pO_2, increase in cortical pCO_2, followed after a delay by hyperemia similar to that seen in A, again followed by late fluctuation in pH.

for that purpose. In some experiments, loose ligatures were placed around the middle cerebral artery, both jugular veins, and both carotid arteries so that they could be occluded as desired by traction.[4] Stroboscopic stimulation was provided by means of a strobolux stroboscopic stimulator.[5] Cortical blood flow was recorded by means of thermistors placed on the cortex.[5] An increase in cortical temperature indicated increased flow, and vice versa. Alveolar CO_2 was recorded by means of a Liston-Becker alveolar CO_2 analyzer. In some

experiments, the arterial oxygen saturation was recorded with an ear oximeter. Blood pressure was recorded by a catheter placed in the femoral artery and connected to a Statham strain gauge. Epileptic seizures were induced by the cortical application and intravenous injection of 10% strychnine sulfate. Cotton wick electrodes were placed on the cortex for recording electroencephalograms. Blood pressure, electroencephalogram, and alveolar CO_2 concentration were recorded on the same graph with an Offner Type D or Type R polygraph.

Cortical *p*H, pCO_2, and pO_2 electrodes. The *p*H electrodes we have used have been either a microglass *p*H electrode thrust into the brain[6] or a small (3-mm. surface contact) Beckman glass electrode originally designed for use during gastric intubation. With either electrode, most satisfactory recordings were made when the output was coupled to a Radiometer* or Beckman N 1 *p*H meter connected in series to a galvanometer and recorded on the polygraph by means of a photovoltaic pickup.[7] The Radiometer or Beckman model N 1 *p*H meter was found to be more satisfactory than the Beckman model G 1, since the signal varies in a linear manner with the *p*H and calibration can be performed with a single buffer solution of *p*H 7.0.

In the first few experiments, separate pO_2 and pCO_2 electrodes were used. *The pO_2 electrode* consisted of a polarographic anode (silver–silver chloride) and cathode (platinum), both of which were immersed in a few drops of saline surrounded by a polyethylene film 10 μ thick resting on the cortex. This electrode unit has a surface diameter of 1 mm. and is similar in principle to the larger electrode designed by Clark[8] for measuring the pO_2 of the blood. The polarographic principle is the same as that used for open tip electrodes inserted into the brain,[1–3,9,10] but the polyethylene film permits absolute measurement of pO_2 in millimeters of mercury. A potential of 0.7 volts was maintained between anode and cathode, and the output from the polarograph was recorded on the Offner Type R dynograph by means of a DC input coupler and balancing device. The electrode gives a linear response for different pO_2 readings and is calibrated at

*If Radiometer *p*H meter is used, the output can be connected directly to the polygraph without the photovoltaic pickup.

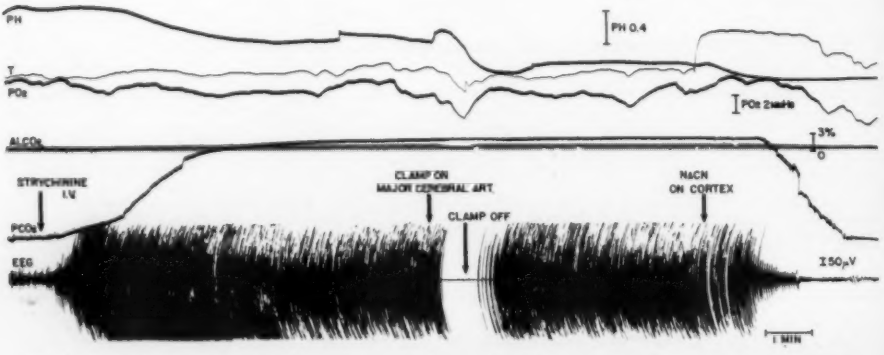

Fig. 2. Strychnine seizures induced in curarized monkey under local anesthesia while cortical pH, blood flow (T), pO_2, and pCO_2 and alveolar CO_2 ($ALCO_2$) and electroencephalogram were recorded. At onset of seizure, cortical pO_2 is reduced, cortical pCO_2 rises, and alveolar CO_2 increases. Arrows indicate where clamp was temporarily placed on all cerebral branches of aortic arch, resulting in decreased cortical blood flow, near zero levels of cerebral pO_2, and flat electroencephalogram. Cortical pCO_2 remained high. When vessels were released, cortical blood flow and pO_2 rose and seizures resumed. When sodium cyanide (NaCN) was placed on cortex, electroencephalographic activity and pCO_2 decreased with decrease in blood pressure (not appearing on record for technical reasons); cortical pO_2 first rose and then fell as cortical blood flow decreased with fall in blood pressure. Transient rise of T at application of NaCN is artifact. Initial pO_2 estimated to be 8 to 10 mm. Calibration of pO_2, *p*H, alveolar CO_2, electroencephalogram, and time are marked on record. Initial pCO_2 is estimated at 40 mm. Hg, but exact pCO_2 calibration is not known since amplifiers were changed after calibration. Irregular rise in *p*H record one and one-half minutes before application of clamp was a temporary artifact.

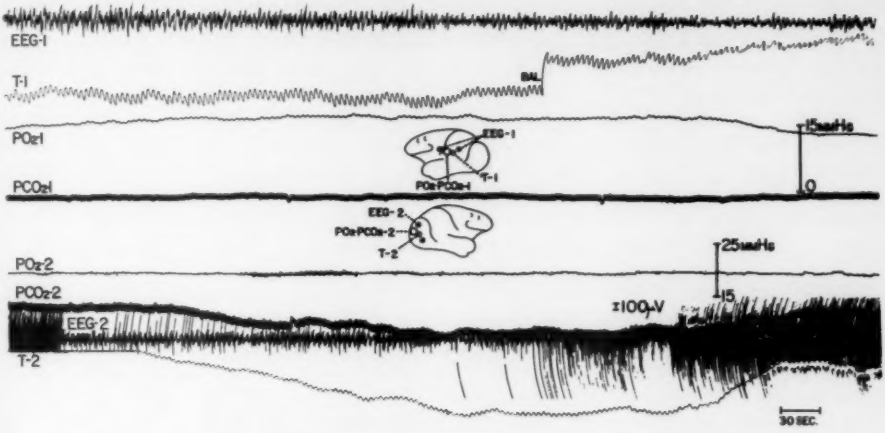

Fig. 3. Focal strychnine seizure induced in occipital lobe of curarized monkey while local electroencephalogram, blood flow (T), pO_2, and pCO_2 were recorded from occipital and opposite Sylvian areas concurrently. Note that electroencephalographic spike activity is localized to occipital area (all electrodes marked 2) and does not occur in Sylvian area (all electrodes marked 1). At beginning of record, focal seizure is terminating and occipital pCO_2 and blood flow decrease; at end of record, focal seizure resumes with increase in occipital pCO_2 and T. In spite of hyperemia, Sylvian pO_2 decreases but occipital pO_2 reduction is negligible because of local hyperemia. BAL indicates that baseline of Sylvian blood flow electrode was mechanically raised by balancing device. Electrode positions are shown on brain diagrams. Calibration of time, electroencephalogram, and pO_2 electrodes are noted on record. Fluctuations in pCO_2 of occipital lobe are in the order of 10 mm., but absolute readings are not available since baseline was changed. Initial rise in brain pCO_2 during onset of seizure is partially obscured by electroencephalographic record.

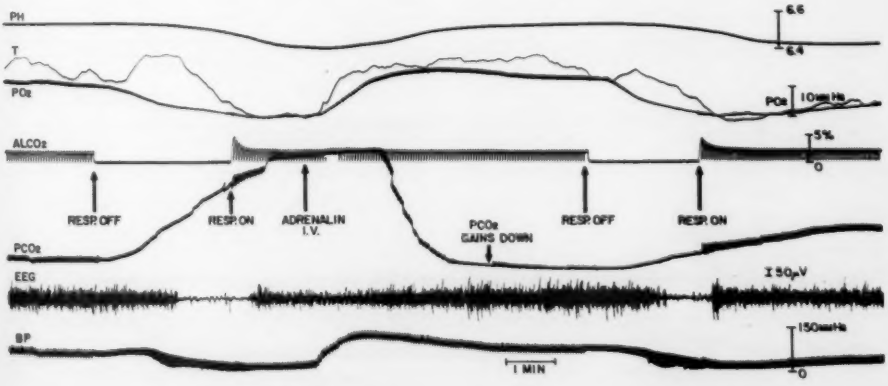

Fig. 4. Monkey immobilized with d-tubocurarine, with local anesthesia and artificial respiration. Effect of asphyxia induced by turning off respirator for two to three minutes. Alveolar CO_2 recording ceases, brain pO_2 and *pH* fall, and brain pCO_2 rises. Cortical blood flow first rises, then falls as blood pressure falls. Electroencephalogram becomes flat, and changes in pO_2 and pCO_2 tend to level off since cerebral metabolism is reduced. When artificial respiration is resumed, pO_2 and *pH* rise, electroencephalographic activity is restored, and brain pCO_2 falls as normal circulation and respiratory exchange are established. Respirator was turned off a second time at lower gains of pCO_2 to show brain pCO_2 curve without distortion (see text for further explanation). Initial pO_2 readings estimated to be 12 mm. Hg. Calibrations of *pH*, pO_2, alveolar CO_2, blood pressure, electroencephalogram, and time are noted on record.

34 to 35° C. in a water bath since, under the conditions of our experiments, the temperature of the exposed cortex is maintained at 34 to 35° C., the body temperature at 36° C., and the room temperature at 24° C. It is important that calibration of the oxygen electrode should be made at the same temperature as the cortex since with our apparatus a change of 1° C. may result in an error of 7 mm. Hg. Providing the blood pressure was well maintained, thermistor readings did not show changes in cortical temperature greater than 0.1° C. during the experiments even when a major cerebral vessel was temporarily occluded, so that absolute values of pO_2 reported here are believed to be accurate to 0.7 mm. Hg. Calibration of electrodes was made immediately before each experiment with saline solutions having a pO_2 of 0, 15, and 53 mm. Hg.

The pCO_2 electrode consisted of a small *p*H electrode, having a surface diameter of 2 to 3 mm., immersed in a few drops of 0.001 N $NaHCO_3$ and surrounded by a polyethylene membrane 10 μ in thickness which enclosed the silver–silver chloride reference electrode. The signals from the CO_2 electrodes were either connected to electrometer couplers and directly recorded by the Offner Type R polygraph or recorded by means of a Radiometer or Beckman *p*H meter coupled in series with a galvanometer, the optical output of which was recorded by means of a photovoltaic cell and the Offner polygraph.[7] The latter method has 2 advantages: [1] absolute values can continually be checked with the *p*H meter, and [2] high amplification is possible with minimal interference. The construction of the pCO_2 electrode is modified after that described by Stow, Baer, and Randall[11] and by others.[9,12–14]

Combination pO_2–pCO_2 electrode. Recently, we have combined both electrodes into a single unit consisting of the polarographic

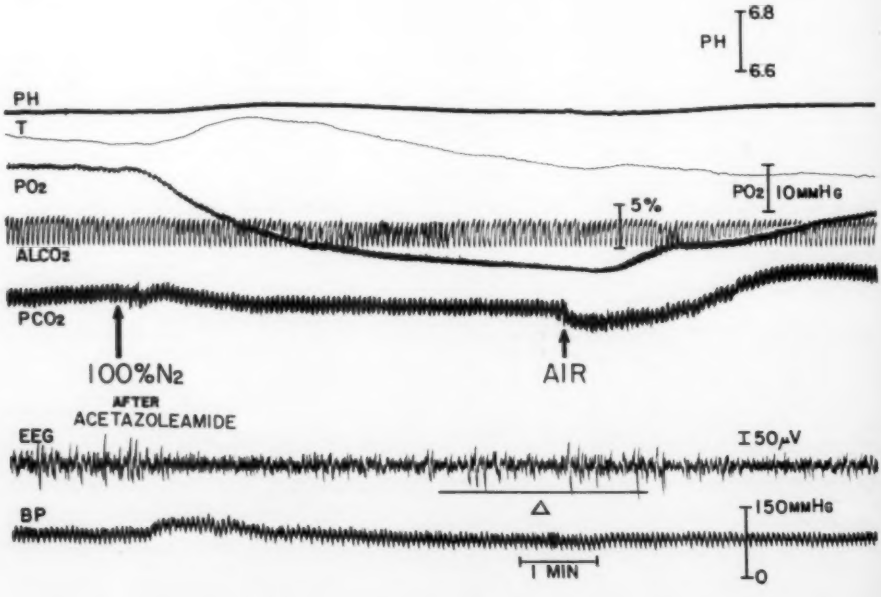

Fig. 5. Anoxia in monkey producing increased cortical blood flow without increased brain pCO_2. 500 mg. of acetazoleamide injected intravenously previously abolished any cerebral vasodilator action due to pCO_2. Nitrogen breathing for five to six minutes reduced cortical oxygen from initial estimated level of 22 mm. Hg to zero, with desynchronization of electroencephalogram followed by slowing and reduction of brain pCO_2 tension. Cortical blood flow increased in spite of reduced brain pCO_2 tension. Cortical *p*H showed slight alkaline shift. Calibration of *p*H, pO_2, alveolar CO_2, blood pressure, electroencephalogram, and time are shown on record. Exact brain pCO_2 calibration is not known since amplifiers were altered after calibration.

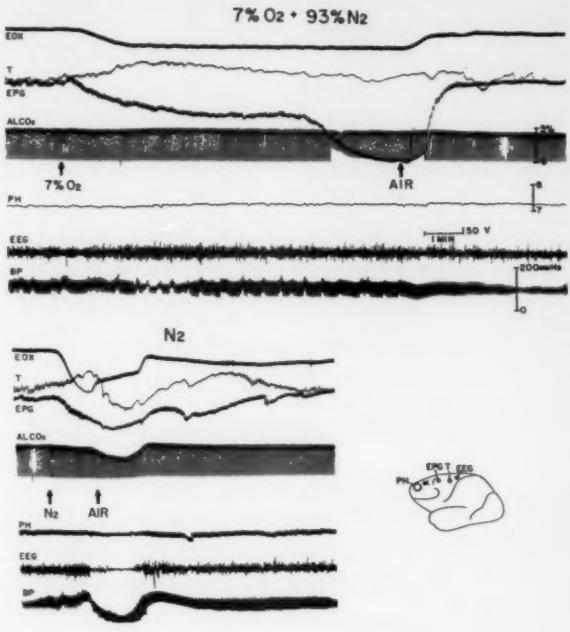

Fig. 6. Effects of 7% oxygen and 93% nitrogen breathing (upper record) compared with 100% nitrogen breathing (lower record) in monkey. EOX=Arterial oxygen saturation recorded with ear oximeter. EPG=Relative cortical oxygen tension recorded with open tip polarograph electrodes. pH=Cortical pH. $ALCO_2$ = Alveolar CO_2. T = Cortical blood flow. Brain diagram at lower right shows electrode positions; black circles indicate electroencephalographic electrode positions. 7% oxygen breathing shows cortical hyperemia (T) which tends to decrease after several minutes, resulting in more severe cortical anoxia, in spite of no further change in arterial oxygen saturation. Baseline of electropolarogram was raised between upper and lower records. Lower record shows much steeper fall in arterial oxygen saturation with brief nitrogen breathing and severe cortical hypoxia in spite of increased cortical blood flow (T). Electroencephalogram becomes isoelectric. With resumption of air breathing, all parameters return to steady state.

anode and cathode plus the *p*H electrode and its silver—silver chloride reference electrode.[20] The combination is immersed in a few drops of 0.001 N $NaHCO_3$ solution or a mixture of 50 cc. of 0.001 $NaHCO_3$ added to 50 cc. of normal saline to which 1 drop of a saturated solution of KC1-AgC1 is added and is covered by a thin polyethylene film. This combined electrode has a rapid initial response time of three to four seconds for both pO_2 and pCO_2. It is stable for thirty to sixty minutes after calibration and has the advantage that a single unit records both pCO_2 and pO_2 from an area of cortex having a surface diameter of only 2 mm. In many experiments, concurrent records were made of cortical blood flow, pCO_2, pO_2, and electroencephalogram in different areas of the brain during various procedures.

RESULTS

General observations. The polyethylene bag eliminates from the pO_2 records the electroencephalographic artifacts occasionally seen when open tip oxygen electrodes were used.[10] Normal determinations for the pial surface of the cortex for cat and monkey were as follows: pO_2 = 10 to 20 mm. Hg (higher if the electrode rests on a large artery or vein); pCO_2 = 23 to 68 mm. (depending on the respiratory exchange of both lung and brain tissue); *p*H = 7.0 to 7.5 units (usually 0.1 to 0.3 units lower than *p*H of arterial blood). The *p*H at the depth is lower, reading 6.7 to 7.2 units. The surface is more alkaline, possibly because CO_2 is lost to the surrounding air at the surface or tissue *p*H is more acid or because trauma during insertion of the electrode in the depths results in acidity. If the dura is widely removed, the pCO_2 readings are lower and recordings are less satisfactory due to loss of CO_2 to the surrounding air.

Breathing of 100% oxygen for one and one-half minutes causes a rise in brain pO_2 to 35 mm. Hg or higher, a decrease in cortical blood flow, and no large change in brain pCO_2 or *p*H.

Effects of electroencephalographic activation. Increased neuronal activity (as judged by activation of the electroencephalogram) resulted in increased cortical pCO_2 and reduced corti-

cal pO_2; these changes were soon followed by increased cortical blood flow, which reversed the metabolic deficit, increasing local pO_2 and decreasing cortical pCO_2. Such changes may be localized to the occipital lobe occasionally after stroboscopic stimulation alone (Fig. 1A) and regularly when strychninization of the occipital cortex is combined with stroboscopic stimulation. Corresponding fluctuations in cortical *p*H occurred due to changes in pCO_2 tension. A similar but diffuse cortical change was seen after an arousal reaction which may be elicited in the drowsy animal by hand claps or turning on the lights in a darkened room (Fig. 1B). Ingvar[9] has reported similar changes during arousal elicited by brain-stem stimulation.

Effects of seizures. Seizures induced by intravenous strychnine decreased the cortical pO_2 and *p*H but increased the cortical pCO_2 with resulting hyperemia (Fig. 2). Localized cortical seizures induced by strychnine caused localized increase of pCO_2 and decreased pO_2 followed by localized hyperemia (Fig. 3). Clamping of the subclavian, innominate, and carotid arteries at the aortic arch during a seizure caused a prompt fall in cortical blood flow, pO_2, and *p*H with cessation of the cortical spike activity in spite of a high pCO_2 of the cortex (Fig. 2). When the vessels were unclamped, the cortical blood and cortical pO_2 were restored and the seizure resumed. The application of sodium cyanide to the cortex abolished the spike activity with flattening of the electroencephalogram, resulting in a temporary rise in pO_2 and a marked fall in pCO_2 of cortex. The cortical pO_2 became decreased terminally.

Effects of anoxia. *Asphyxia.* When artificial respiration was discontinued in the curarized animal, resulting asphyxia produced a highly reproducible series of events (Fig. 4). The

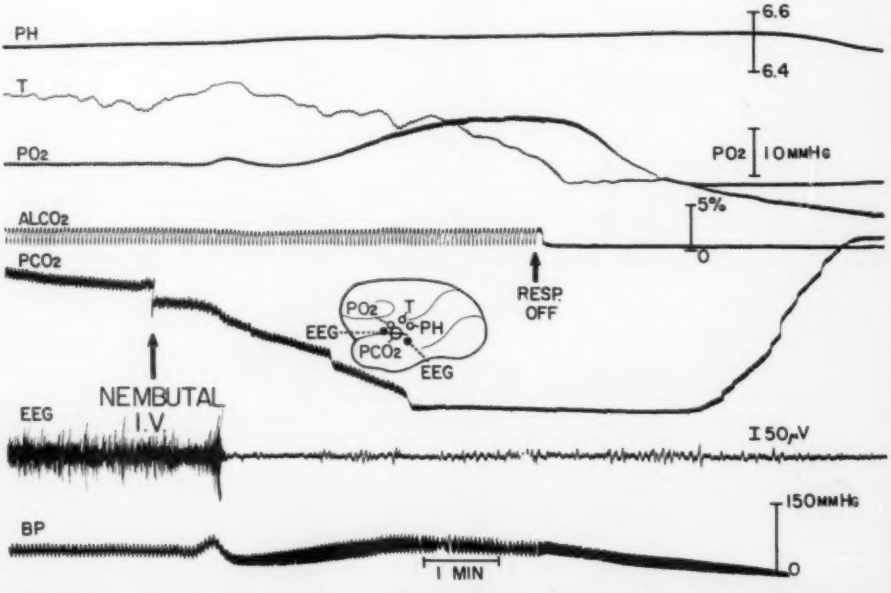

Fig. 7. Effects of intravenous Nembutal in curarized monkey under local anesthesia. Electrode positions are shown on brain diagram. Intravenous injection of 120 mg. of Nembutal results in decreased electroencephalographic activity, increased pO_2 levels, decreased cortical pCO_2 (with alkaline *p*H change), and reduced cortical blood flow. When respirator is turned off, brain pCO_2 rises terminally due to CO_2 accumulation in blood with asphyxia. Calibration of *p*H, pO_2, alveolar CO_2, electroencephalogram, blood pressure, and time are shown on record. Exact calibrations of brain pCO_2 are not available.

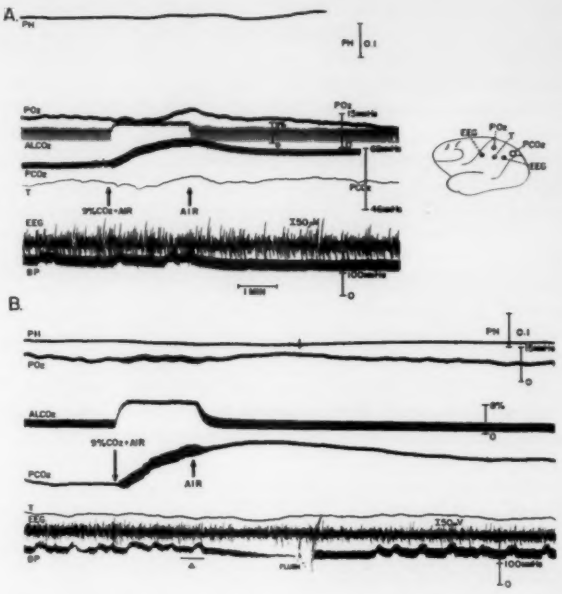

Fig. 8. Effects of breathing mixture of 9% CO_2 and air for two minutes before and after intravenous injection of acetazoleamide in monkey. [A] Before acetazoleamide, 9% CO_2 breathing produces rise in alveolar CO_2 and brain pCO_2 with increased cortical blood flow and cortical oxygen tension. Cortical *p*H fluctuates correspondingly. [B] After 500 mg. of acetazoleamide intravenously, 9% CO_2 breathing for comparable period of time produces rise in alveolar CO_2 and brain pCO_2, without any significant change in cortical blood flow, and slight rise in cortical pO_2. Cortical *p*H shows slight acid change. Calibrations of cortical *p*H, pO_2, alveolar CO_2, brain pCO_2, electroencephalogram, blood pressure, and time are shown on record.

brain pCO_2 rose (due to progressive CO_2 retention in the blood), and the cortical blood flow increased, but, in spite of this, the cortical pO_2 fell to zero levels with flattening of the electroencephalogram. After the electroencephalogram flattened, the brain pCO_2 showed a plateau since metabolic production of CO_2 was now reduced. When artificial respiration was resumed, the brain pO_2 increased, the electroencephalogram was restored, and the brain pCO_2 showed a further rise. However, the blood pressure had fallen due to the asphyxia, and epinephrine was necessary to restore the blood pressure and cortical blood flow. When cortical blood flow was increased after the injection of epinephrine, tissue pCO_2 was rapidly reduced since stagnant blood flow was restored to normal.

Breathing of 100% nitrogen rapidly reduced tissue pO_2 to near zero levels and resulted in slowing of the electroencephalogram, with a small rise in blood pressure (Fig. 5). Usually, initial desynchronization of the electroencephalogram occurred.[15] The cortical blood flow increased due to the vasodilator effect of anoxia, independent of the influence of carbon dioxide since cortical pCO_2 remained unchanged or became *decreased* due to increased blood flow. The *p*H showed little change or became slightly alkaline since pCO_2 was decreased. Resumption of air breathing restored the cortical oxygen tension, the electroencephalogram became normal, and pCO_2 production of the brain was restored.

Breathing of 7% oxygen. The importance of the vasodilator effect of anoxia on cerebral vessels is shown in Figure 6, where changes in oxygen tension at a depth of 3 to 7 mm. were recorded with open tip electrodes. Breathing of 7% oxygen produced a prompt reduction in both brain oxygen tension and arterial oxygen saturation without any significant change in brain *p*H. Shortly after 7% oxygen breathing was begun, cortical blood flow increased and the oxygen saturation of the arterial blood remained constant at reduced level. After seven minutes, cortical hyperemia began to fail; consequently, cortical oxygen fell precipitously in spite of the absence of further change in arterial oxygen saturation. Shortly thereafter, 100% nitrogen breathing (Fig. 6) produced a comparable but more serious train of events.

The arterial oxygen saturation was reduced precipitously. Brain pO_2, which was already low, fell in a comparable manner but not as precipitously as the arterial oxygen saturation of the blood, since cortical blood flow became increased. Eventually, there was a fall in blood pressure and the electroencephalogram became flat. As the electroencephalographic activity ceased, brain pO_2 levels tended to reach a plateau because metabolic demand for oxygen was reduced. The alveolar pCO_2 became temporarily decreased due to decreased pulmonary circulation during hypotension. Resumption of air breathing after nitrogen reversed the sequence; the arterial oxygen saturation promptly rose, and the blood pressure and brain pO_2 returned to normal levels with restoration of the electroencephalogram.

Effects of decreased cerebral metabolism. *Cyanide.* In Figure 2, it may be seen that cyanide applied to the brain during a seizure abolished the electroencephalographic discharge and decreased cortical pCO_2 production; hence, brain pCO_2 was decreased. In other experiments, the same sequence occurred when cyanide was applied to normal cortex. The application of cyanide to the normal brain results in a rise in brain pO_2 since cortical metabolic demand for oxygen is reduced. Such decreased cerebral metabolism is followed by a decreased cortical blood flow since both decreased brain pCO_2 and increased brain pO_2 result in local vasoconstriction.

Barbiturates. During recording with regional anesthesia and curare, the effects of deep barbiturate anesthesia were studied. Figure 7 shows the effect of the intravenous injection of 120 mg. (30 mg. per kilogram) of Nembutal. The electroencephalogram initially showed

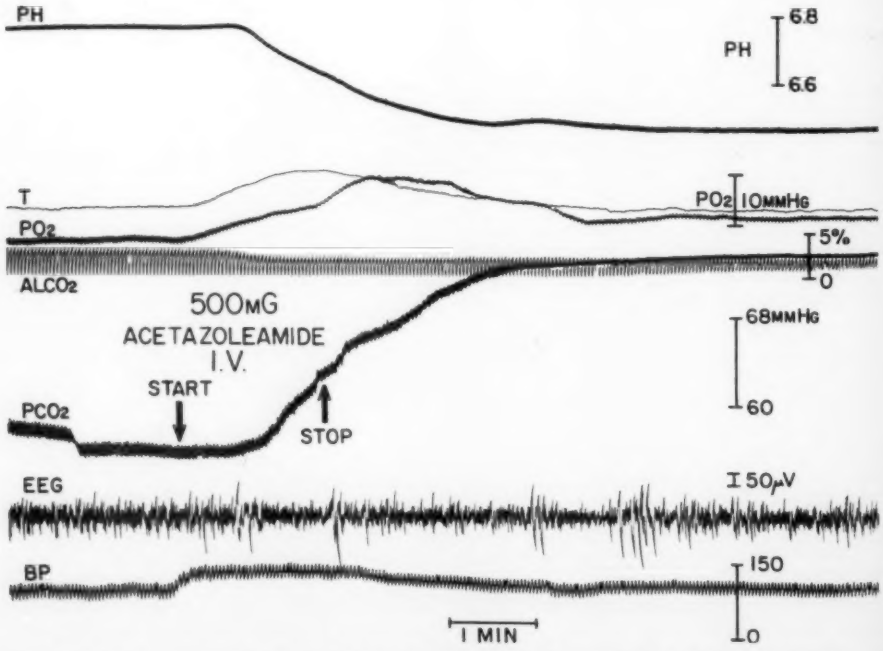

Fig. 9. Effect of intravenous injection of 500 mg. of acetazoleamide in monkey. Blood pressure rose during injection. Acetazoleamide reduced alveolar CO_2 level and produced increased brain pCO_2 and marked cortical acidity. Rise in cortical blood flow and pO_2 occurred. Calibrations of *p*H, pO_2, alveolar CO_2, brain pCO_2, electroencephalogram, blood pressure, and time are shown on record. After injection, rise in pCO_2 recorder was limited by full pen deflection.

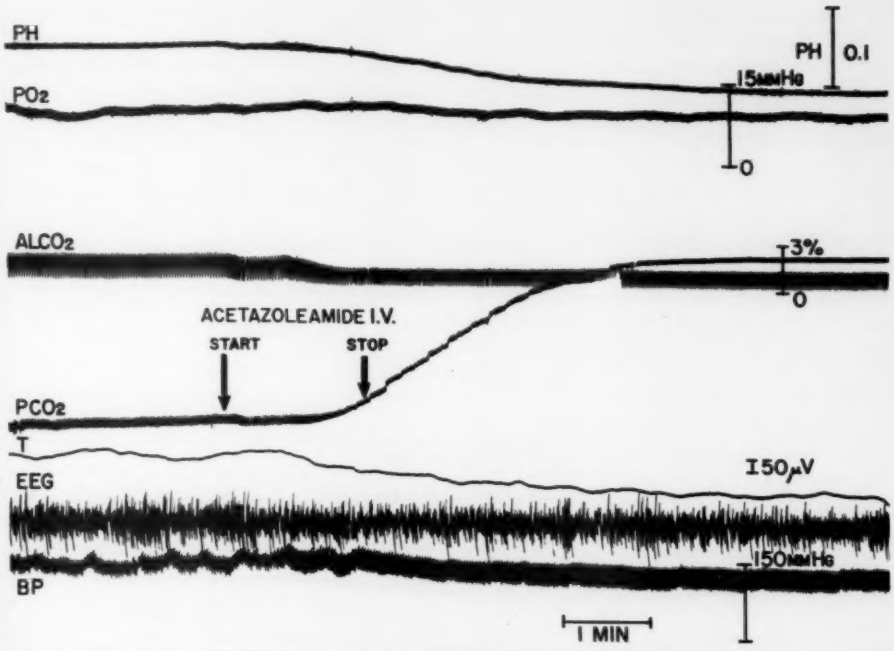

Fig. 10. Effect of repeated intravenous injection of 500 mg. of acetazoleamide in monkey without any rise in blood pressure during injection. Acetazoleamide reduced alveolar CO_2 level and increased brain CO_2 level and cortical acidity, but cortical blood flow was not increased and cortical pO_2 was unchanged. Calibration of *p*H, pO_2, alveolar CO_2, electroencephalogram, blood pressure, and time are shown on record. Exact pCO_2 calibrations are not available.

high voltage slowing followed by extremely low voltage activity in the delta range. As the electroencephalographic activity and neuronal metabolism subsided, brain pO_2 increased, brain pCO_2 rapidly declined, and, finally, cortical blood flow decreased. The *p*H showed an alkaline shift due to the decrease in cortical pCO_2. Light barbiturate anesthesia produced little metabolic change in spite of the appearance of spindles in the electroencephalogram.

Effects of carbon dioxide, acetazoleamide, sodium bicarbonate, "carbonic acid," and acetic acid. *CO_2.* The vital influence of blood pCO_2 and brain pCO_2 on the cerebral circulation became more and more evident as these studies progressed. The cerebral circulation can be controlled at will by manipulation of the rate of respiratory exchange and hence the pCO_2 of the circulating blood.[16] Hypocapnea results in vasoconstriction. If hyperventilation is continued long enough, cerebral anoxia and electroencephalographic slowing result.

The effect of breathing a mixture of 9% CO_2 and air for two minutes is shown in Figure 8A. Increase is seen in the alveolar pCO_2, the brain pCO_2 (from 50 to 68 mm. Hg), and the cortical blood flow. The increased cortical blood flow raises the pO_2 of the cortex by 10 to 15 mm. Hg. After the intravenous injection of 500 mg.* of acetazoleamide (Diamox), breathing of 9% CO_2 for two minutes was repeated with comparable results *except* that the cortical blood flow and pO_2 did *not* become increased. We conclude from this and other data that CO_2 has to be converted to HCO_3^- by carbonic anhydrase at

*500 mg. of acetazoleamide is an extremely large dose for the monkey.

the target organ (presumably the vessel wall) before it becomes effective as a relaxant for smooth muscle.

Acetazoleamide. The effect of the intravenous injection of acetazoleamide in monkey cortex is shown in Figures 9 and 10. The effect in the cat was similar. Acetazoleamide is a potent carbonic anhydrase inhibitor, and the intravenous injection of this substance produced remarkable metabolic effects. Alveolar CO_2 gradually decreased because CO_2 tended to become "fixed" in the tissues, transport by the circulating red cells being interfered with. Brain pCO_2 showed a remarkable increase often exceeding 20 mm. Hg. In Figure 9, the cortical *p*H showed a decrease from 6.78 to 6.5 with some slowing of the electroencephalogram. Blood pressure rose during venepuncture, with an increase of cortical pO_2 and blood flow preceding the injection. Usually, as in Figure 10, where the blood pressure did not rise in spite of the marked increase in brain pCO_2, there was no increase in cortical blood flow. Usually, cortical blood flow increased when small doses of acetazoleamide were given. As mentioned previously, acetazoleamide blocks the conversion of CO_2 to H^+ and HCO_3^-, thus preventing its effectiveness as a vasodilator factor. The entire series of events following acetazoleamide injection was in keeping with the known pharmacologic actions of this drug. CO_2 was not converted into HCO_3^- in the red cell so that it was not transported rapidly from the tissues by the venous circulation. Concurrent measurements of arterial *p*H showed a delayed increase in hydrogen ion concentration, although alveolar CO_2 decreased within thirty seconds. The

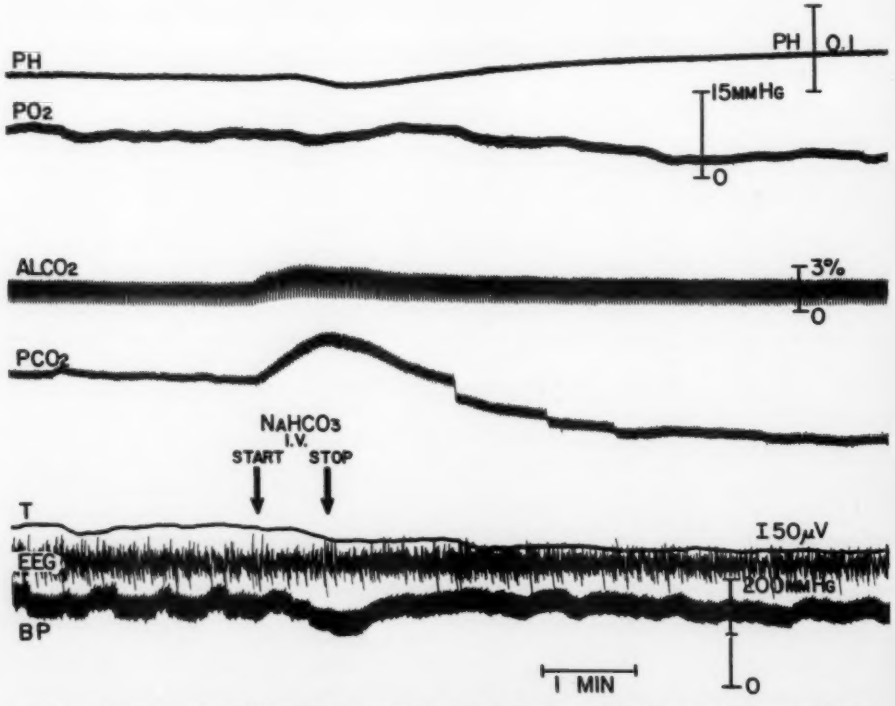

Fig. 11. Acetazoleamide abolishing cerebral vasodilator effect of sodium bicarbonate in monkey. 500 mg. of acetazoleamide had been injected intravenously previously. Between 2 arrows, 45 mEq. of sodium bicarbonate was injected intravenously, resulting in increased alveolar CO_2 level and brain pCO_2, with an acid change in cortical *p*H but no increase in cortical blood flow or pO_2. Calibration of cortical *p*H, pO_2, alveolar CO_2 ($ALCO_2$), electroencephalogram, blood pressure, and time are shown on record.

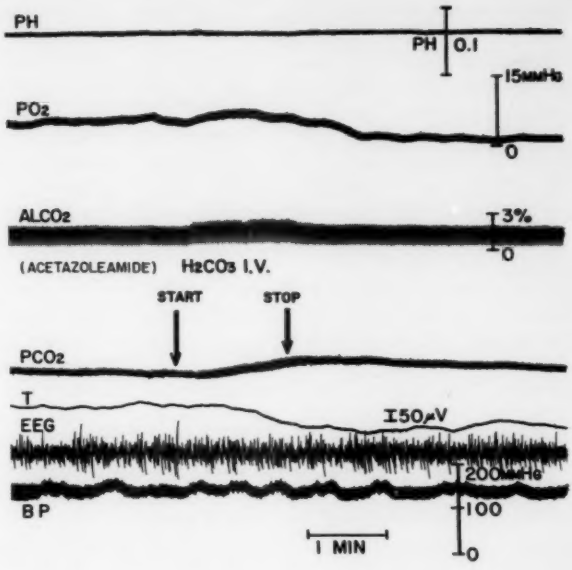

Fig. 12. Acetazoleamide abolishing cerebral vasodilator effect of intravenous injection of "carbonic acid" in monkey. 500 mg. of acetazoleamide had been injected intravenously previously. Between arrows, 15 cc. of 25% solution of "carbonic acid" was injected intravenously. Alveolar and brain CO_2 increased, but cortical blood flow did not. Calibration of cortical *p*H, pO_2, alveolar CO_2 ($ALCO_2$), electroencephalogram, blood pressure, and time are shown on record.

arterial acid shift gradually developed after a delay of three to five minutes and was presumably due to loss of alkali reserve ($NaHCO_3$) by the kidney. After intravenous injection of acetazoleamide, carbonic anhydrase inhibition appeared to be relatively greater in the red cell than in the brain, since brain *p*H became acid more rapidly than the arterial blood and reflected the brain pCO_2 change. Brain pCO_2 increased because transport of CO_2 by the red cells of the cerebral venous capillaries was impaired and the CO_2 produced by tissue metabolism tended to accumulate. Excess brain tissue CO_2 combined with water to form H^+ and HCO_3^-, resulting rapidly in brain tissue acidity in spite of carbonic anhydrase inhibition.

Sodium bicarbonate. Under normal conditions, the intravenous injection of sodium bicarbonate solution resulted in an increase in brain pCO_2 and alveolar CO_2, with an alkaline shift of brain *p*H and an *increase* in cortical blood flow and pO_2. After large doses of acetazoleamide, the injection of sodium bicarbonate produced the same series of events except that cerebral vasodilation did *not* occur (Fig. 11), so, apparently, HCO_3^- ion in the circulating blood is not the effective agent.

"Carbonic acid." The intravenous injection of "carbonic acid" (approximately 25% solution of frozen CO_2 in water*) in the intact animal produced increased alveolar CO_2, brain pCO_2, cerebral blood flow, and cortical pO_2. After large doses of acetazoleamide (Fig. 12), the intravenous injection of the same amount of carbonic acid produced a comparable increase in alveolar and cortical pCO_2, but there was no increase in cortical blood flow or cortical pO_2. To all appearances, endovascular CO_2 is ineffective when carbonic anhydrase is inhibited.

Acetic acid. The intravenous injection of a weak solution of acetic acid during metabolic alkalosis (such as by the intravenous injection of sodium bicarbonate) produced an increase in alveolar CO_2 and brain pCO_2 because sodium bicarbonate in the blood stream combines with the acetic acid, resulting in the liberation of CO_2. This was accompanied by a fall in brain *p*H and increased blood flow; when acetic acid was injected intravenously after acetazoleamide, *little or no* increase in cortical blood flow occurred in spite of the

*Solid CO_2 (25 gm.) was dissolved in 100 cc. of water in a beaker with a loose plastic top. The solution was warmed to body temperature, and 10 cc. was injected.

increase in cortical pCO_2 (Fig. 13) because conversion to HCO_3^- was blocked.

Effects of vascular occlusion. *Occlusion of the superior vena cava.* When the venous outflow from the brain was obstructed by clamping of the superior vena cava (Fig. 14) or by occlusion of both jugular veins, there was a reduction in cortical blood flow and a rise in cortical pCO_2 due to stagnation, with a corresponding decrease in cortical *p*H. Cortical pO_2 was reduced, and there was slowing in the electroencephalogram which appeared to result from accumulation of acid metabolites and cortical anoxia. Alveolar CO_2 was also reduced. When the clamp was released, cortical blood flow was restored, brain pCO_2 returned to resting levels, and the electroencephalogram improved.

Carotid artery occlusion. When both common carotid arteries were occluded in the monkey, the cortical blood flow and cortical pO_2 were reduced, the latter by 6 to 7 mm. Hg, and cortical pCO_2 rose markedly due to slowed blood flow. The cortical *p*H became acid, corresponding to the accumulation of CO_2 (Fig. 15). When the clamps were removed, cortical blood flow again increased, cortical pO_2 increased, and cortical pCO_2 returned to resting levels with a corresponding rise in cortical *p*H.

Total cerebral ischemia. If the innominate, subclavian, and carotid arteries were clamped in the thorax when the cortical pO_2 was already reduced due to low blood pressure, as in Figure 16, cortical blood flow was further reduced; cortical pO_2 fell until the electroencephalogram became isoelectric and then rose because cerebral metabolism was decreased or ceased. Cortical pCO_2 also increased, but cortical *p*H decreased. When blood flow was restored, cortical blood flow, pO_2, pCO_2, and *p*H returned to the steady state. If this pro-

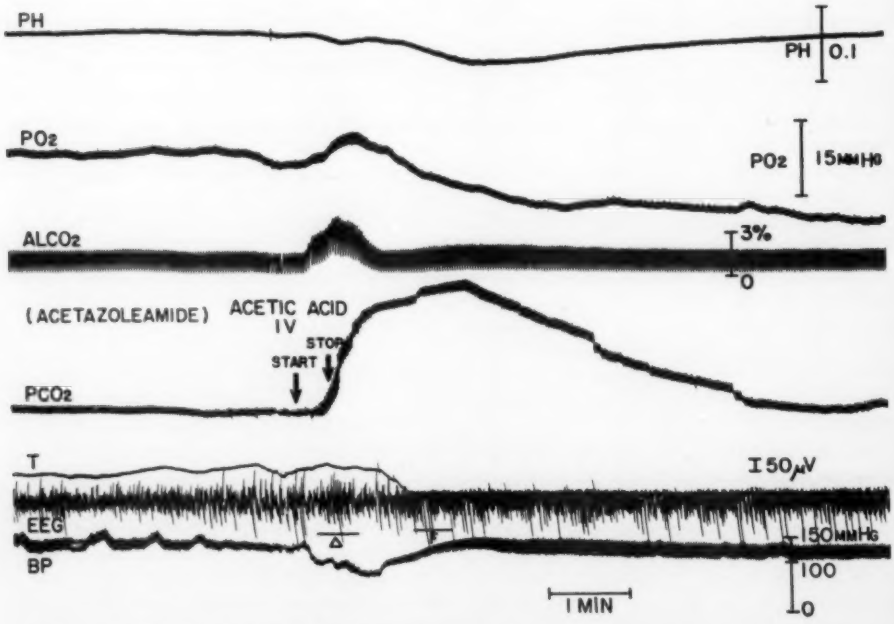

Fig. 13. Acetazoleamide abolishing cerebral vasodilator effect of intravenous injection of acetic acid after sodium bicarbonate. 500 mg. of acetazoleamide and 45 mEq. of sodium bicarbonate had been injected previously. Dilute solution of acetic acid was injected between 2 arrows, increasing alveolar pCO_2 and causing transient slowing of electroencephalogram; brief increase in cortical blood flow was followed by improved electroencephalographic activity as metabolic acidosis improved. As electroencephalographic activity increased, cortical pO_2 decreased.

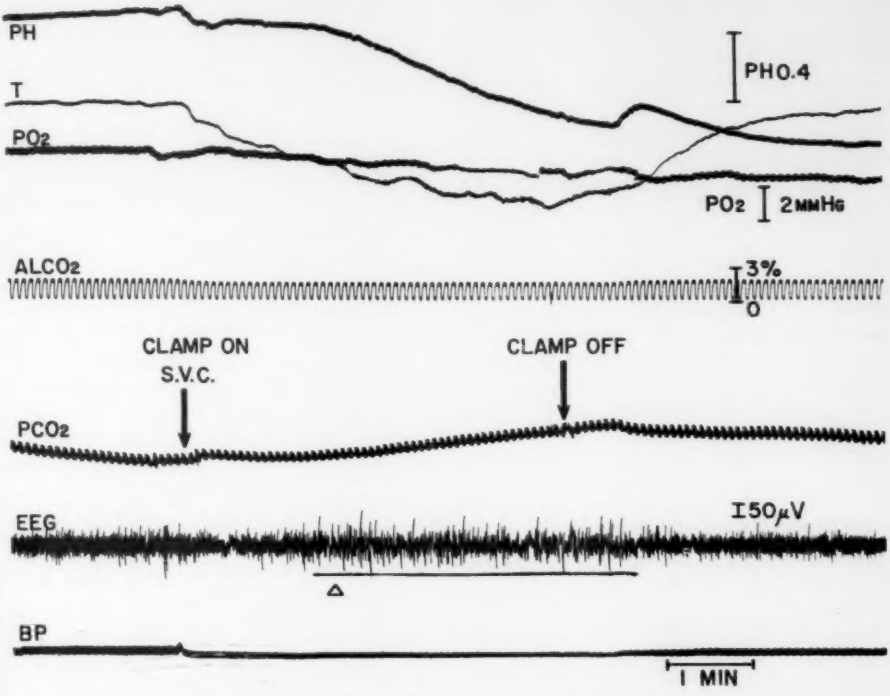

Fig. 14. Effect of clamping superior vena cava in monkey. Blood pressure was low (about 60 mm. Hg), cortex was already acid, and cortical pO_2 levels were low. Clamp was applied between 2 arrows resulting in decreased cortical blood flow (T), increased cortical pCO_2, and marked cortical acidity. Electroencephalographic slowing was apparently due to combination of hypoxia and accumulation of acid metabolites. Calibration of *p*H, pO_2, alveolar CO_2, electroencephalogram, and time are shown on record. Initial pCO_2 level is estimated at 40 mm. Hg.

cedure was repeated when cortical pO_2 was at or near zero levels, as in Figure 17, a point was reached at which cerebral anemia resulted in prompt further slowing and reduced amplitude of electroencephalographic activity, with a rise in cortical pO_2 and a fall in cortical pCO_2 because cerebral metabolism was minimal or absent. However, this state of metabolic arrest was reversible for many minutes.

Middle cerebral artery occlusion. When the middle cerebral artery was occluded intermittently by means of a ligature[4] while records of pO_2, pCO_2, *p*H, electroencephalogram, and blood flow were made from both the Sylvian area and the occipital lobe, the Sylvian pO_2 became reduced to 0 to 2 mm. Hg while the occipital lobe pO_2 remained normal or slightly elevated (20 mm. Hg). The occipital pCO_2 tended to increase to high levels (53 mm.) due to slowed blood flow, while the Sylvian pCO_2 fell to low levels due to lowered cerebral metabolism and CO_2 production. These changes preceded slowing of the electroencephalogram (delta activity) recorded from the Sylvian area. Each time the middle cerebral artery was occluded, the cortical blood flow, pO_2, and pCO_2 in the Sylvian area became reduced while the cortical blood flow, pCO_2, and pO_2 in the bordering area showed an increase. Breathing a mixture of 6% CO_2 and air tended to improve the cortical blood flow and pO_2 in the ischemic area by causing further vasodilation in the border zones.

Intravenous injection of hypertensin. It has been shown previously[17] that the intravenous injection of hypertensin, the circulatory vaso-

constrictor factor present with renal hypertension, causes intense cerebral arterial constriction. Figure 18 shows the effect of injecting 1 mg. of hypertensin slowly into the femoral vein. The blood pressure rose, and the arterioles constricted from 80 to 50 μ. The pial blood flow and pial oxygen tension decreased concurrently, and the electroencephalogram showed slowing. In this experiment, the brain pCO_2 decreased and the *p*H became alkaline, presumably because of decreased cerebral metabolism.

Intravenous injection of epinephrine. The rise in blood pressure after intravenous injection of epinephrine, particularly if the blood pressure is low, is followed by increased cortical blood flow and cortical pO_2 and decreased cortical pCO_2 due to an increased rate of venous flow. Only with severe hypercapnea, such as follows large doses of sodium bicarbonate, does the injection of epinephrine result in an increased brain pCO_2, since then the pCO_2 is higher in the blood than in the brain.

DISCUSSION

Influence of cerebral metabolism on blood flow. As a result of these experiments, it became apparent that a homeostatic mechanism exists within the brain whereby local increases in metabolic demand tend to result in local hyperemia. A diagram which summarizes such a mechanism, as revealed by these experiments, is shown in Figure 19. Any stimulus—such as an arousal response, photic driving by the use of photic stimulation, strychninization of the cortex, or a seizure produced by a convulsant drug—which appeared to us to increase cerebral metabolism resulted in increased met-

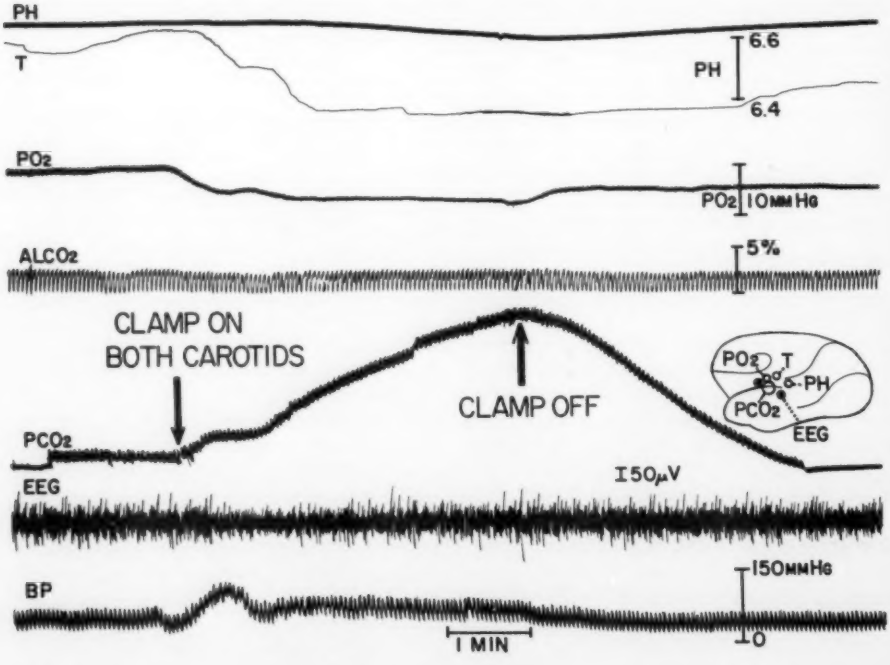

Fig. 15. Effect of bilateral common carotid artery occlusion (between arrows) in monkey. Blood pressure and initial pO_2 levels are higher than in Figure 14. Electrode positions are shown on brain diagram. After carotid occlusion, cortical pCO_2 rose, both cortical pO_2 and blood flow (T) decreased, and cortical *p*H became slightly acid. Electroencephalographic change was minimal since cortical hypoxia was less severe than in Figure 14. Calibration of *p*H, pO_2, alveolar CO_2 ($ALCO_2$), electroencephalogram, blood pressure, and time are shown on record.

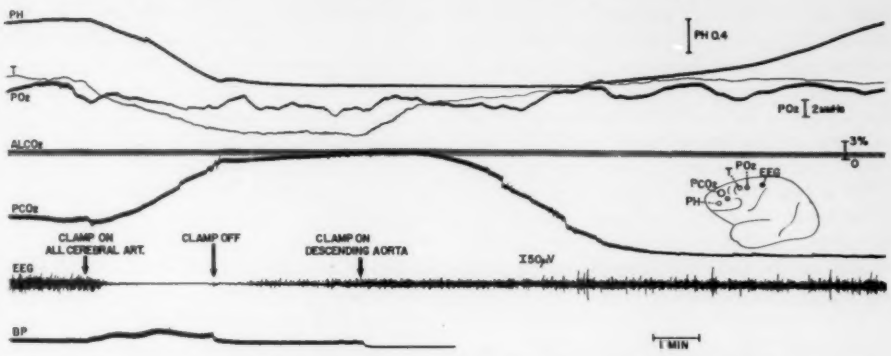

Fig. 16. Effect of total cerebral ischemia produced in monkey by clamping all cerebral vessels at arch of aorta. Cortical pO_2 level (6 to 8 mm.) and blood pressure were low at start of experiment. All cerebral arteries were clamped at first arrow, resulting in fall in cortical blood flow (T), marked cortical acidity (pH), and rise in cortical pCO_2, with fall in cortical pO_2. Electroencephalogram became flat, and cortical pCO_2 and pO_2 curves tended to show a plateau. Clamp was then released, with small rise in cortical pO_2 and return of electroencephalogram; blood pressure remained low, so descending aorta was clamped in order to increase cerebral blood flow. Hence, femoral blood pressure no longer was recorded. After this maneuver, cortical blood flow increased, cortical pCO_2 fell, electroencephalogram reverted to normal, and cortical pH returned to steady state. Small fall in pO_2 before first arrow indicates partial occlusion of arteries during manipulation within mediastinum.

abolic production of CO_2 followed, after a delay of sixty to ninety seconds, by local or generalized increase in cerebral blood flow. We believe that local increase in CO_2 is the important vasodilator factor and that the latency represents the time for the gas to diffuse to the arteriolar net; we presume that there the CO_2 diffuses through the vessel wall and is converted by carbonic anhydrase into HCO_3^-, resulting in relaxation of smooth muscle. Thus, when sodium bicarbonate solution is injected intravenously, CO_2 is liberated, diffuses through the cell membranes of the vessel wall, and is then converted again by carbonic anhydrase to H^+ and HCO_3^-, either of which ions may relax the arterial smooth muscle. This general principle is confirmed by the fact that, if hyperventilation is performed during localized hyperemia (that is, after strychninization of occipital lobe producing a localized seizure), the decrease of brain pCO_2 and blood flow is greater in the area of hyperemia than elsewhere in the brain. The fact that the CO_2 effect may be local is confirmed by the fact that alveolar CO_2 levels do not increase during photic stimulation, local strychninization, or arousal but do increase with systemic increases in blood CO_2 tension. Brief inhalation of 6% CO_2 can be utilized to raise brain pCO_2 to levels comparable to those seen after arousal or photic stimulation, and this results in comparable increases of cerebral blood flow. However, the latency for vasodilation after inhalation of CO_2 is shorter (fifteen to thirty seconds) than when a local increase of brain pCO_2 results from increased cerebral metabolism. The differences in latency suggest that the effects of endovascular CO_2 are more rapid, presumably because diffusion is less from within the vessel wall than from surrounding tissue outside. Furthermore, endovascular CO_2 exerts the dominant effect on cerebrovascular resistance when compared to the influence of pCO_2 of brain tissue, for, under certain circumstances such as hyperventilation after infusion of sodium bicarbonate, it is possible to note progressive cerebral vasoconstriction as the endovascular CO_2 becomes reduced while brain pCO_2 rises.

The general subservience of local cerebral blood flow to local metabolic demand is aided to some degree by the reduction of tissue pO_2 that accompanies increased metabolic activity, since local anoxia also causes vasodilation. However, this factor is less important than CO_2. Once local increases in metabolism result in local hyperemia, a very sensitive homeostatic mechanism adjusts blood flow to

meet local needs, for vasodilation itself decreases pCO_2 and increases pO_2 and hence vasodilation ceases.

Conversely, cortical blood flow is decreased in states of anesthesia and in states of reduced cerebral metabolism such as drowsiness, provided respiration is not slowed as during sleep, with respiratory hypercapnea and cerebral vasodilation. In these conditions, cortical CO_2 production and oxygen utilization are reduced, with a fall in tissue pCO_2, a rise in pO_2, and consequent vasoconstriction. As discussed earlier, carbonic anhydrase seems to be necessary for CO_2 to exert its vasodilator influence.

Hemodynamic homeostasis in the brain. This series of experiments has revealed a mechanism whereby, under normal physiologic conditions, the cerebral circulation is able to compensate for minor changes in hemodynamics secondary to systemic changes such as increased blood pressure or cardiac output. The mechanism is summarized diagrammatically in Figure 20. For example, a rise in blood pressure due to intravenous injection of epinephrine or to spontaneous fluctuations is followed by increased cortical blood flow; this increase in turn decreases cortical pCO_2 and increases cortical pO_2, resulting in a compensatory reduction in blood flow. On the other hand, a fall in blood pressure results in increased cortical pCO_2 and decreased cortical pO_2, producing compensatory vasodilation. This mechanism provides an adjustment for small changes in hemodynamics. If there are large changes in blood pressure, accompanying wide variations in intraluminal pressure have a direct effect on the arteriolar smooth muscle by a stretch reflex.[17] This stretch reflex originally described by Bayliss results in vasoconstriction when there is a large rise in blood pressure and in vasodilation when it falls.

Hemodynamics and metabolism in ischemia. When local cerebral blood flow is reduced—for example, after occlusion of the middle cerebral or common carotid arteries in the monkey—the brain pCO_2 increases and brain pO_2 decreases in the ischemic area. If collateral blood flow is sufficient, as is the rule after occlusion of the common carotid artery, the increase in brain pCO_2 as well as the reduction of intraluminal pressure results in vasodilation and increased blood flow to the ischemic area; compensation occurs, with a return of tissue pO_2 and pCO_2 to normal levels (Fig. 21). When the middle cerebral artery is occluded or ruptured, particularly if the blood pressure

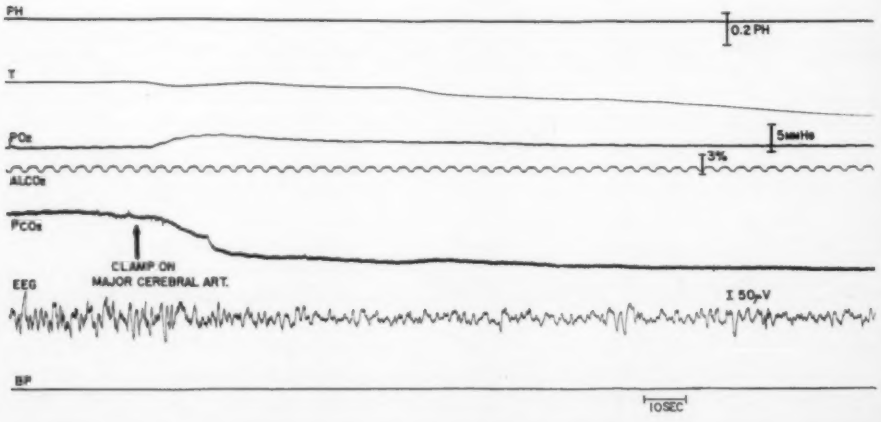

Fig. 17. Effect of clamping all cerebral branches of aortic arch in monkey, with low blood pressure, cortical pO_2 levels near zero, and electroencephalographic slowing already present. Vessels were clamped at arrow, and electroencephalogram showed further slowing and reduced amplitude; cortical oxygen rose, and cortical pCO_2 fell (reduced CO_2 production) in spite of further reduction of cerebral blood flow (T), indicating, we believe, reduced metabolism. Calibration of cortical *p*H, pO_2, alveolar CO_2, electroencephalogram, and time are shown on record.

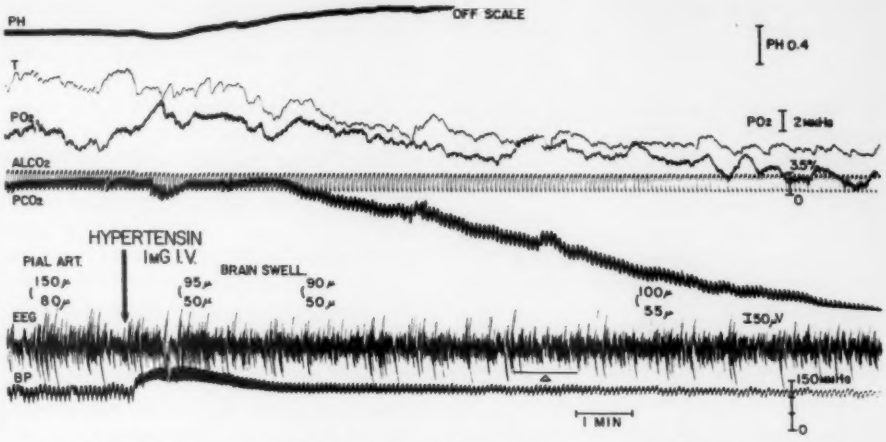

Fig. 18. Effect of intravenous injection of 1 mg. of hypertensin (vasodepressor factor in renal hypertension) in monkey. Brain was also being observed with dissecting microscope, and any brain swelling and measurements of pial arteries were noted on the record. As hypertensin was injected, systolic blood pressure rose to 175/135 and 2 pial arteries measuring 150 and 80 μ, respectively, constricted to 90 and 50 μ. Brain appeared swollen. Cortical blood flow and cortical oxygen tension became progressively reduced, cortical pCO_2 fell, and cortical *p*H rose. Electroencephalogram showed slowing.

is low, the collateral blood flow is insufficient and there is a rise in tissue pCO_2 and a progressive fall in tissue pO_2 to near zero levels (0 to 6 mm. Hg) in the Sylvian region. If brain tissue pO_2 persists for many minutes at such low levels, oxygen is insufficient to maintain normal cerebral metabolic activity and electroencephalographic slowing results. Under such circumstances, there is a localized decrease in cerebral metabolism with decreased CO_2 production and oxygen utilization. Consequently, tissue CO_2 tension is reduced and the pO_2 tension fluctuates at low levels. If the collateral circulation is finally restored after delays of as long as fifteen minutes or more by raising the systemic blood pressure, the local pO_2 tension rises and the electroencephalographic activity and normal metabolic activity are restored; these changes are followed by a rise in brain tissue pCO_2 and a fall in brain pO_2. If the collateral circulation is not restored, irreversible infarction results, with continued low pCO_2 and high pO_2 levels. The exact time required for infarction to result varies with the degree of ischemic anoxia, but, with severe ischemia, it may become manifest within forty-five minutes. In all areas of severe localized ischemia or infarction, there is a bordering area of active metabolism with high tissue pCO_2 and low pO_2. Both these metabolic factors tend to cause vasodilation and increased collateral blood flow in the border zone. Concurrent *p*H records in bordering and ischemic areas show that the ischemic and infarcted areas become acid, usually reflecting accumulation of CO_2 in the tissue. In most experiments, increases of collateral flow have followed changes in pCO_2 rather than in *p*H. In this respect, local blood flow in the cat and monkey brain follows changes in pCO_2 more closely than those in *p*H, as has been shown to occur in man.[18] These experiments do not exclude the possibility that certain acid metabolites produced in areas of ischemia may have specific vasodilator effects.[19]

In the study in which epileptic seizures have been induced, we have confirmed the observations of Ingvar that tissue pCO_2 is greatly increased during seizure activity, but, whenever the seizures have been terminated by vascular occlusion or decreased cerebral blood flow (as in Figure 2), their termination has usually appeared to be due to the reduction of the cortical pO_2 and rarely to the accumulation of acid metabolites. This supports the view that postepileptic paralysis and the peri-

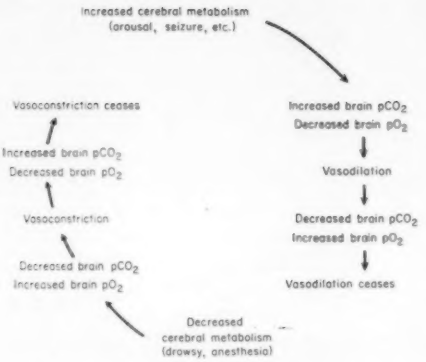

Fig. 19. Schematic diagram of mechanisms of metabolic circulatory homeostasis in brain

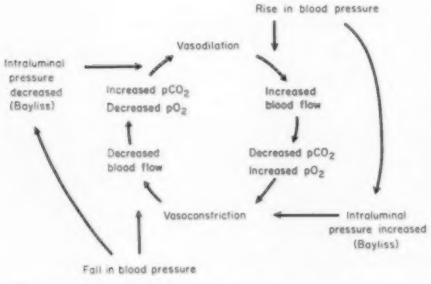

Fig. 20. Schematic diagram showing mechanisms of hemodynamic homeostasis in brain

odicity of seizures usually are related to tissue anoxia rather than to accumulation of acid metabolites.[10]

Throughout these experiments in which pO_2, *p*H, and pCO_2 levels have been recorded concurrently in different areas of the brain and have been correlated with the electroencephalogram and records of local blood flow, it has been apparent that cerebral metabolism and respiratory exchange influence cortical blood flow. Conversely, cerebral metabolism may be affected by alterations in cortical blood flow. Such observations have made it posisble to define a homeostatic mechanism within the brain whereby local changes in metabolism are able to regulate local changes in blood flow. These same regulatory mechanisms tend to aid the collateral circulation in areas of ischemia. The most important single factor is increase in pCO_2, which occurs in all ischemic areas and has salutary vasodilatory effects.

CONCLUSIONS

1. Absolute measurements of cortical *p*H, pCO_2, and pO_2 in different areas of the brain have been correlated with localized changes in blood flow, electroencephalographic activity, blood pressure, and alveolar carbon dioxide concentration. Combined electrodes covered by a thin layer of polyethylene were used, and both absolute pO_2 (polarograph electrodes) and pCO_2 (*p*H electrodes) of an area of the cortex were continuously recorded.

2. Normal values of cortical tissue pO_2 varied between 10 and 20 mm. Hg with the animal breathing air. pCO_2 readings from the same area varied between 23 and 68 mm. Hg, depending on respiratory exchange. *p*H values varied between 7.0 and 7.5 units.

3. Certain changes in electroencephalographic activity (activation with stroboscopic stimulation, strychnine application, and arousal reaction) resulted in decreased cortical pO_2 and increased pCO_2 followed by cortical hyperemia, which tended to restore pO_2 and pCO_2 levels toward normal.

4. Seizures induced by strychnine decreased cortical pO_2 and *p*H but increased the cortical pCO_2 with resulting hyperemia. When the seizures were inhibited by ischemia, the inhibitory effect was due primarily to anoxia rather than increased pCO_2.

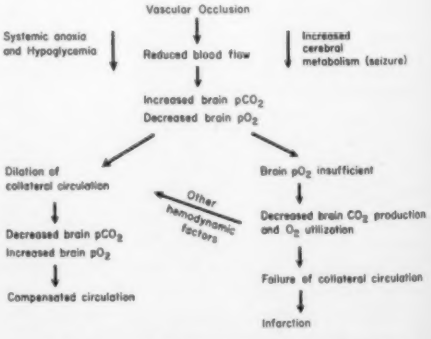

Fig. 21. Changes in hemodynamics and metabolism during cerebral ischemia

5. During nitrogen breathing, cerebral vasodilation was due to anoxia, since reduction of cortical oxygen tension was unaccompanied by a rise in pCO_2.

6. Decreased cortical activity due to cyanide, barbiturates, drowsiness, or ischemic anoxia resulted in an increase in tissue pO_2 and a fall in brain pCO_2.

7. Inhalation of carbon dioxide or the intravenous injection of sodium bicarbonate or "carbonic acid" produced increased cortical blood flow. The intravenous injection of acetazoleamide resulted in a rise in brain pCO_2 and inhibited the vasodilator effects of carbon dioxide, sodium bicarbonate, and "carbonic acid." Increased pCO_2 in the blood or diffusion to the cerebral vessels from brain tissue caused vasodilation, but carbonic anhydrase appeared necessary to produce the vasodilator effect.

8. Cerebral venous occlusion resulted in a fall in brain pO_2 and a rise in brain pCO_2.

9. Cerebral arterial occlusion resulted in a fall in brain pO_2 and a rise in brain pCO_2 in the territory of supply. These changes stimulated the collateral blood flow. If cortical pO_2 fell to near zero levels, electroencephalographic slowing and reduced cortical metabolism resulted, with lowered pCO_2 and increased pO_2 levels. If collateral circulation was improved, normal metabolism tended to be restored; if collateral circulation failed, the cortical pO_2 fell to zero and cerebral infarction resulted.

10. There appeared to be a homeostatic mechanism within the brain whereby cerebral metabolism regulated local metabolic requirements. The most important single factor in this mechanism was local CO_2 production.

This work was supported by grants from the National Institute of Neurological Diseases and Blindness and the Research Corporation of the Detroit Receiving Hospital.
Dr. Gotoh is a fellow of the Michigan Heart Association. The authors are indebted to Mr. Peter Miller for technical assistance.

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Discussion on vascular flow and turbulence

William E. Stehbens, M.B., B.S., D.Phil.

I HAVE NO CRITICISM to make of the interesting observations that have just been discussed. My own interest in cerebral hemodynamics is related to the changes in the cerebral arteries which might subsequently lead to serious interference with cerebral metabolism and function. Therefore, some brief comments I will make have a bearing on the subject under discussion.

In a study of the histologic changes in the cerebral arteries of fetuses and infants, thickening of the intima, which is generally regarded as preceding atherosclerosis, was found only in relation to the sites of branching of the arterial tree. The intimal proliferation did not occur diffusely about each fork but as separate pads which later coalesced.[1] In the terminology described previously,[2] the facial and dorsal pads were the earliest to be seen and the lateral pads next. The apex was the last site about the fork to be affected. Such a localization of the pads suggested that their etiology might be dependent on hemodynamic factors, because the apical and lateral pads occured at sites where stream lines might separate from the vessel wall and where eddy currents might occur. Consequently, the possibility of turbulence in the cerebral arteries was investigated.

Some authors have considered that, under normal conditions, turbulence of flow would not occur in the cerebral arteries at the base of the brain[3–6] and, in fact, not even in the vascular system as a whole, except possibly at the root of the aorta.

The reason for this was that the Reynolds number (Re) calculated for the mean velocity of flow would only exceed the critical figure of 2,000 in the aorta under special circumstances. When the Re was less than 2,000, the flow was believed to be laminar or smooth. The Re is computed from the equation:

$$\mathrm{Re} = \frac{\rho \mathrm{VD}}{\mu}$$

ρ is the density of the liquid, V is the velocity, D is the diameter of the vessel, and μ is the absolute viscosity of the liquid.

The belief was based on the work of Reynolds,[7] who studied the transition of laminar or steady flow to sinuous or turbulent flow of water in straight glass tubes. Coulter and Pappenheimer[8] found by experiment that the critical Re for bovine blood in a straight tube was about 2,000. In other words, the critical Re for both blood and water appeared to be the same for similar conditions of flow—hence the belief that 2,000 was the critical value for flow in the vascular system.

The hypothesis that laminar flow prevailed in the vascular system therefore was studied by performing experiments on glass models as analogues of the cerebral arteries.[9] The first model consisted of a glass tube bent into an S-shape to resemble the carotid siphon of the internal carotid artery. The 4 other models were branched tubes with varying angles of bifurcation. A steady flow of water under a constant pressure was delivered to the model, and turbulence of flow was examined at different velocities by the dye injection technic. In this way, the approximate critical Re for each model was determined during forward and reverse flow.

In the straight tubing, the critical Re was approximately 2,000. At lower velocities, turbulence was induced in the S-shaped curve, wide angled bifurcations, and at the unions of the streams when the Re was often considerably less than 2,000. During forward flow

in the models with a narrow angle of bifurcation, definite turbulence did not occur below 2,000.

The application of these experimental findings to the human circulatory system suggests that 2,000 is not the critical Re throughout the vascular tree, which is complicated with numerous and often wide branchings. The critical Re would have to be estimated individually for any particular site, and values well below 2,000 would be common.

Calculation of Reynolds numbers for the mean velocity of arterial flow overlooks the fact that the flow is pulsatile. The Re calculated for the peak velocity would be considerably greater than values for the mean velocity. As turbulence may be induced intermittently,[10] the Re at the peak velocity is important, particularly in view of the findings of McDonald,[11] who demonstrated turbulence in the rabbit aorta occurring intermittently at the peak velocity of flow.

Reynolds numbers calculated for the human aorta under physiologic conditions will be over 11,000 for the peak velocity and considerably higher during strenuous exertion. Theoretically, turbulence could also occur at forks in smaller arteries and also in veins. The critical Re for the S-shaped curve in the experiments mentioned[9] was about 500, so that turbulence might well occur in the carotid siphon. In the model fork with an angle of bifurcation of 180°, the critical Re was about 350. Therefore, unsteady flow is likely to be induced in the anterior cerebral artery which arises at a reflex angle. Hence, it would seem highly likely that turbulence occurs in the major cerebral arteries of the adult. What occurs in the infant and fetus is unknown, and the relationship of turbulence to the changes at the forks in the cerebral arteries is still obscure.[12]

Some additional observations have been made in vessels smaller than those which I have been discussing. A local increase in the width of the marginal or plasma zone has been observed at the apex of the union of two streams in the small vessels of the rabbit ear chamber. This local increase occurs at a site in which intimal thickening occurs in the larger vessels of infants. It resembles a separation of stream lines from the vessel wall where stagnation and eddy currents might occur in larger vessels. Slow flow is also to be seen at the apex of bifurcations of vessels in the rabbit ear chamber; individual red cells, which usually move so fast that they cannot be distinguished, may be seen to hesitate and be held against the apex before being washed away into either branch. Increase in width of the marginal plasma zone was not observed at the lateral angles, as might be expected, though such an occurrence was seen in one vessel which divided and subsequently reunited. Here, the marginal plasma zone was wider at the lateral aspects of the configuration, while the cellular or axial zone was displaced medially. This was not a regular feature, and what happens in the facial and dorsal areas cannot be visualized.

Whether such flow patterns have any relation to that in larger vessels and to the intimal changes is unknown but warrants further investigation.

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Quantitative measurement of regional metabolism, pO_2, and pCO_2 in the cerebral cortex

David H. Ingvar, M.D.

WITH THEIR NEW TECHNICS, Drs. Meyer and Gotoh have excellently illustrated the changes in blood flow, pO_2, and pCO_2 in the cerebral cortex which accompany alterations in its functional activity, as well as changes of respiration and systemic circulation.

In the present discussion, I should like to bring up some *quantitative* aspects of tissue measurements with pO_2 and pCO_2 electrodes. I will also give a short summary of some new technics recently developed for a quantitative determination of regional cerebral (cortical) metabolism in vivo. Although our group has so far only been carrying out studies on the cerebral cortex, it is our hope that our methods may be used in other parts of the central nervous system—as well as in other organs, for that matter—for quantitative in vivo studies of the complex normal and pathologic interplay among functional activity, blood flow, and metabolism in a relatively small tissue volume.

The results to be presented in this summary were obtained during the course of a collaborative study which has been going on for about a year and a half at the Laboratory of Clinical Neurophysiology, Department of Neurology, University of Lund, Sweden. In this team work, which is sponsored by the Swedish Medical Research Council and the Deutsche Forschungsgemeinschaft, my associate, Dr. B. Siesjö, and myself have been fortunate enough to collaborate with a distinguished group of foreign colleagues, Doz. Dr. D. Lübbers and Dr. U. Gleichmann from Cologne, Doz. Dr. G. Thews from Kiel, and Dr. N. A. Lassen from Copenhagen.

QUANTITATIVE ASPECTS OF MEASUREMENTS WITH pO_2 AND pCO_2 ELECTRODES IN BRAIN TISSUE

Recent developments of the membrane-covered platinum cathode[1] and the membrane-covered *p*H electrode for pCO_2 measurement[2] have made stable electrodes available for quantitative tissue pO_2 measurements[3–5] and for quantitative tissue pCO_2 measurements.[6,7] By the use of such electrodes, measurements can be carried out upon the surface of the cerebral cortex with minimal interference with functional conditions. Due to their size (active area, 3 to 5 mm. in diameter), such electrodes integrate a gas tension over a relatively large cortical area. They do, in fact, give a reasonably good measurement of the *mean* tissue pO_2 and tissue pCO_2, respectively, as we have found.

It seems important to emphasize here that any value of pO_2 or pCO_2 measured by a surface electrode on the cerebral cortex cannot be interpreted unless information is available on a number of factors. The most important are [1] capillary geometry, [2] diffusion coefficients for respective gases in the tissue and blood, [3] the actual arterial and cortical venous pO_2 and pCO_2, and, also, [4] the metabolic rate of the tissue. With such information, the tissue gas tension measured can be related to a *mean tissue tension* calculated from the tissue diffusion model originally worked out by Krogh[8]—the so-called tissue cylinder.[9–11] Recently, Thews[11] has given an extensive theoretic and experimental analysis of oxygen diffusion in the brain. With Siesjö,

he has also studied the diffusion of carbon dioxide and its physicochemical characteristics in the gray matter of the cortex.[12]

Using tissue electrodes 4, 6, and 7 on the surface of the cerebral cortex in a series of experiments upon anesthetized (Nembutal) cats and dogs at steady state, we also determined the pO_2 and pCO_2 in arterial and cortical venous blood. For the blood determinations, we used the technics developed by Lübbers and Gleichmann[13] (Severinghaus and Bradley[14]). The cortical venous samples were obtained from a small cannula in the superior sagittal sinus close to outlets from veins coming from the cortical region, where the pO_2 and pCO_2 electrodes and the blood flow meter were placed. All the diploic anastomoses to the sinus had been eliminated operatively, of great importance for the venous sampling technic.

When placed upon the cortical surface, the pCO_2 electrodes[6,7] measured a value closely similar to the calculated actual mean tissue pCO_2. Measurements with quantitative tissue pO_2 electrodes[4] also indicated that they measure a mean tissue pO_2 as calculated according to Thews[11] from the tissue cylinder model. These findings would, it seems, be of great importance in a further analysis of phenomena recorded by the electrodes in continuous measurements during, for example, changing cortical functional conditions. Drs. Meyer and Gotoh showed a number of examples of such phenomena which soon, it seems, after further technical development, can be quantitatively analyzed.

QUANITATIVE DETERMINATION OF REGIONAL CORTICAL OXYGEN CONSUMPTION

Several studies in recent years have emphasized the necessity of developing methods for a *regional* determination of the cerebral metabolism in vivo.[10] With the advancement of the tissue pO_2 and pCO_2 measuring technics, it became highly desirable to develop a more simple method for quantitative determination of regional cerebral blood flow. The methods hitherto existing for this purpose, developed by Kety and his associates,[15] only permitted one measurement per tissue per experiment, since they required decapitation of the experimental animal.

In collaboration with Dr. Lassen, we have recently developed a repeatable (semicontinuous or continuous) quantitative method for regional blood flow determination by the use of krypton-85.[16] This method has been used in experiments in rabbits, cats, and dogs for measurements on the cerebral cortex. It has been found to yield a determination of the average blood flow in cubic centimeters per gram per minute in an area measuring 5 mm. in diameter and about 0.5 mm. in depth, with

DETERMINATIONS OF REGIONAL TISSUE GAS TENSIONS, BLOOD FLOW, AND METABOLIC RATE IN THE POSTSIGMOID GYRUS OF THE DOG

	Series I	Series II (One hour later)
Arterial blood		
Samples taken from femoral artery		
pO_2 (mm. Hg)	84.0	81.0
Volume % O_2	21.8	17.9
pCO_2 (mm. Hg)	44.5	50.0
Volume % CO_2	33.6	37.5
*p*H	7.270	7.205
Temperature (° C)	38.6	39.1
Cortex		
Diameter of area measured, 3 to 5 mm.; depth, 0.3 to 0.6 mm.		
pO_2 (mm. Hg)	42.0	42.0
pCO_2 (mm. Hg)	48.0	(62)*
Cortical blood flow† (cc. per gm. per minute)	0.71	0.90
Temperature (° C).	38.5	39.0
Cortical venous blood		
Samples drawn from small cannula mounted in superior sagittal sinus		
pO_2 (mm. Hg)	38.5	41.7
Volume % O_2	11.2	9.3
pCO_2 (mm. Hg)	54.0	72.5
Volume % CO_2	44.7	46.6
*p*H	7.190	7.155
Calculations		
Arteriovenous difference		
O_2	10.6	8.7
CO_2	11.1	9.1
Respiratory quotient	1.05	1.06
Regional cortical oxygen consumption (cc. per 100 gm. per minute)	7.5	7.8

*Represents a calculated value
†Mean of 3 determinations made two minutes before, during, and three minutes after blood samples were taken

an over-all accuracy of about 10%. Our determinations in anesthetized cats have shown a good agreement with regional values of cortical blood flow obtained by Kety, Sokoloff, and their associates.[15]

Our group recently employed the technics briefly reviewed above in a series of experiments in dogs (Nembutal anesthesia). Repeated determinations of local blood flow were made in the somatosensory area (postsigmoid gyrus) simultaneously with van Slyke analyses of the oxygen and carbon dioxide content of arterial and cortical venous blood. This enabled a calculation of a regional cortical respiratory quotient as well as the regional cortical oxygen consumption. In addition, simultaneous measurements of tissue, arterial, and cortical venous pO_2 and pCO_2 were carried out with the technics mentioned. The details of these experiments will be published shortly.[17,18]*

The table gives an example of the results obtained in 2 such determinations made in 1 experiment in an anesthetized dog at steady state. The preparation was immobilized with Flaxedil, and artificial respiration was used. Determinations were made one hour apart from arterial and cortical venous blood samples and from regional measurements on the surface of the postsigmoid cortical areas (symmetric placement of measuring devices). Arterial samples were taken from the femoral artery. Cortical venous samples were drawn slowly from a small cannula mounted in the superior sagittal sinus (without diploic anastomoses), with its frontal end 8 to 12 mm. from the area where the measuring electrodes and blood flow meter were placed. Note the increase in pCO_2 values from series I to series II. Simultaneously, local cortical blood flow increased. With a stable cortical functional activity during Nembutal anesthesia monitored on the electroencephalogram, the increase in blood flow led to a diminution of the arteriovenous differences of oxygen and carbon dioxide. The respiratory quotient and regional cortical oxygen consumption remained about the same in the 2 series of determinations.

In experiments of the type illustrated, we have made a number of observations on the well-known relationship between blood and tissue pCO_2 and regional blood flow in the cortex.[19,20] As yet, however, we have not studied this relationship systematically. We will therefore, at present, have to abstain from a quantitative correlation between local carbon dioxide production and local blood flow in the cerebral cortex.[21] The existence of such a correlation is, I think, strikingly demonstrated by our findings with continuously recording pCO_2 tissue electrodes.[22] Dr. Meyer also showed some illustrations of this.

It should finally be emphasized that our present results pertain only to certain functional steady states of the cerebral cortex in anesthesia. Further technical development will be necessary in order to determine quantitatively the time relationships between metabolic and circulatory changes taking place during acute alterations in the cortical functional activity. Of especial interest in this connection are states of sleep induction, arousal reactions, and epileptic seizures.[23] Like Drs. Meyer and Gotoh, we have found that such states are accompanied by very conspicuous changes in cortical pO_2 and pCO_2.[22,24,25]

In this symposium on cerebrovascular disease in man, it would seem appropriate to end by expressing the hope that it will soon be possible to apply quantitative technics of the type described directly during craniotomies in man, in order for us to reach a better understanding of metabolic and functional conditions in the diseased human brain.

*The technical assistance of Miss B. Sorensson and Miss A. Plinke is gratefully acknowledged.

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General discussion of afternoon session, April 30, 1960

Dr. Seymour S. Kety, Chairman

DR. KETY: I think it is of some interest to ask to what extent these collaterals, which represent potential anastomotic situations, actually operate in the living state to correct deficits in one or another of the sources of supply.

The only physiologic studies that I know of in man were those of Shenkin, Cabieses, and Copperman some ten years ago. In a relatively few patients, measurements were made of over-all cerebral blood flow before and after ligation of one carotid. These studies suggested that, in the average young individual, complete compensation could be effected by these communicating channels that have been so elegantly discussed today; there was no change in cerebral circulation acutely after a ligation. However, in one elderly individual, there was a significant fall in total cerebral blood flow which was accompanied by clinical changes. These authors also made some calculations of the resistance values in the circle of Willis or in the total communicating channels. Their findings indicated that, in the elderly individual, these resistances were considerably higher than in youth, suggesting that, with development of arteriosclerosis in the larger communicating branches, the efficacy of these collaterals declined.

DR. BERRY: Dr. Baker, in an incomplete, hardly scientific study of brains of psychiatric patients, I found that there was a surprising lack of arteriosclerosis in brains of schizophrenics, even though the patient may have died of coronary artery disease. Have you any information on the mentally ill in hospitals?

DR. SCHEINBERG: It is a little discouraging that Dr. Taylor's comments indicate that, at the present time, we have no means whatever of evaluating this rather difficult and certainly important problem. In Dr. Baker's study, it seems that there is very little correlation between anything at all and cerebral atherosclerosis. Assuming that cerebral atherosclerosis may not be the lesion with which we are concerned, and assuming that what Dr. Taylor said is true, that is, that myocardial infarctions or brain infarctions are not the final events, certainly they are the final clinical events. Are there any kind of clinical correlative studies which indicate that there is a relationship between anything at all and the incidence of brain infarction and what we consider to be clinical cerebrovascular disease?

DR. A. B. BAKER: In our series of cases, we had the usual number of patients with mental illness that one finds in a routine autopsy series. As I recall, it did not seem to make much difference; they seemed to fit into the general pattern of our entire population. I believe that, in doing such a study, one becomes misled as far as clinical impressions are concerned. In the classifying of atherosclerosis, clinical impressions do not always fit as one gets a larger series and the general picture becomes clear. I don't know that we would have a different type of curve than we have for the general population. Mental illness did not seem to make much difference.

I should like to point out that we have dealt with the basic factor of cerebral atherosclerosis. This is an intimal change in the large vessels, which produces a roughening of the inner surface of vessel walls. A clinical study will not tell you what is going on within the vessel wall. Patients in our series who had no clinical symptoms often had the greatest degree and the most severe type of cerebral atherosclerosis at autopsy. The study of the basic process of cerebral atherosclerosis must remain an autopsy problem. When one studies cerebral thrombosis, one encounters an entirely different process. It is not only the proc-

ess of intimal change of the blood vessel but also a thrombotic process superimposed upon an atherosclerotic plaque. This process can be caused by many factors. It may be caused by a change in the blood clotting mechanism. Patients with a minimal degree of cerebral atherosclerosis may still have a thrombus formed on a single plaque of atherosclerosis, with the resulting syndrome of a cerebral infarct or a stroke. This was particularly brought out in our same type of study of coronary disease. We found that 35% of our patients with severe coronary atherosclerosis had no clinical evidence of coronary disease at all. A number of patients, at least 6, who had a minimal degree of coronary disease, a single plaque, died of acute coronary infarction.

We are dealing with a thrombotic process which is quite different from the arteriosclerotic process; one remains a pathologic problem, and the other is a chemical and, perhaps, a clinical problem.

DR. KETY: I should like to ask Dr. Kaplan to come back to the beginning of the session and open his discussion of the subject of collateral circulation.

DR. KAPLAN: I would like to thank the discussers for their comments. Dr. vander Eecken, I believe, asked about the incidence of anterior communicating–anterior cerebral collateral. I think about 90% or more of the patients had large proximal anterior cerebrals and anterior communicatings to care for any collateral circulation, anatomically at least. Actually, it depends not only on its anatomic possibility but also, of course, on the physiologic effects of general blood circulation and atherosclerotic changes.

I would like to recommend Dr. vander Eecken's monograph on the anastomoses between the leptomeningeal arteries of the brain. He has some beautiful pictures which he did not have the time to show today. He stressed the embryology of anastomoses, which I believe is so very, very important.

I have one question for Dr. Sokoloff. In his discussion, he referred to the intracranial pressure as being related to blood flow. I wonder if it is the pressure effects on the brain itself that cause the blood flow change? This was intimated by Dr. Meyer. It seemed more likely to me.

DR. SOKOLOFF: In response to the last question, I think you have raised a very good point. In studies done by Dr. Kety and his associates, in cases of mass intracranial lesions, they found a progressive increase in cerebrovascular resistance which correlated very well with increase in intracranial pressure. The blood flow was not changed, however, because there was also an associated increase in mean arterial blood pressure. There was a critical level, about 400 mm. H_2O, above which the mean arterial blood pressure did not appear to increase in proportion to the increase of cerebral blood flow, and these subjects also happened to be in coma. It is likely that other factors are involved because, in patients like these that are in coma and have low cerebral blood flow, Shenkin and his associates have reduced intracranial pressure acutely by the use of hypertonic glucose solutions or ventricular drainage. They found no improvement of the cerebral blood flow or the clinical state of patients immediately after the procedure. Thus, something else must be involved. I wonder if the reason why these subjects were not improved rapidly is that, when the brain has been subjected to a low cerebral blood flow for a long time, a sudden decrease in the factor which was responsible for reducing the blood flow is not sufficient to restore function to normal. I think in those cases it is quite likely that the blood flow remained low because of low metabolic rate, which resulted in turn from the fact that the brain was temporarily functioning poorly because of the prolonged ischemia. The question of whether intracranial pressure increases cerebrovascular resistance is one that we have inferred from the hydrostatic model. The cerebral vessels are rather thin-walled and are within a relatively closed cavity. It is hard to believe that the pressure of the fluid within the cavity will not impinge upon cerebral vessels, as in the Starling resistance valve, and thus increase the resistance to flow.

DR. KAPLAN: Dr. vander Eecken asked again about the difference in collateral supply if the proximal anterior cerebral and anterior communicating were large. Before going over 50 cases just last week, it was my impression that, if the proximal portion of one anterior cerebral artery was small, the proximal posterior cerebral artery, usually on the same side,

was large. I have seen that association in a number of cases. In going over these 50 specific circles of Willis, I found that less than 10% showed a small proximal anterior cerebral on one side and a contralateral proximal posterior cerebral that was also small. Fortunately, approximately 90% of the cirlces of Willis have large anterior cerebral and anterior communicating arteries and large proximal posterior cerebral arteries to care for any occlusion of a carotid artery on one side.

DR. KETY: There is a question from the floor for Dr. Kaplan.

"Was it not Cohnheim who advanced the principle of the end-arterial supply of the cortex?"

DR. KAPLAN: Actually, there is no true end-artery, that is, an artery that ends abruptly. Every artery ends in a capillary. However, Cohnheim and Temple Fay and all of the rest of them are correct when they say that, once an artery enters into the cerebral substance, it then becomes truly an end-artery. It doesn't give blood to anything else once it enters. The artery is so small at this point that nature seems to demand that it go to the place it is supposed to and supply the cells it is supposed to, without giving blood supply to any other structure. Moreover, once blood enters into the capillary system, it is not conceivable that it would go from one capillary to another capillary but, rather, flows through into the lower pressure venous system. I would say that all the collateral circulation occurs on the surface of the brain and that end-arteries are truly functional end-arteries but are not so anatomically.

DR. KETY: Dr. Baker, several additional questions have been raised.

"You did not mention some of the currently popular concepts of etiology of atherosclerosis in general. Would you comment on the factors of heredity, dietary habits, blood lipids, and lipid metabolism?"

"Can you report on any correlation between cerebral atherosclerosis and retinal artery sclerosis? Similarly, is cerebrovascular disease with hypertension related to retinal hypertensive change? In summary, can one evaluate the status of cerebral vessels by ophthalmoscopy?"

"What is the relationship between arteriosclerosis and clinical thrombosis?"

I was wondering about the very interesting negative correlation between malignancy and arteriosclerosis—whether patients who died of malignancy also died at an earlier age than patients dying of other illnesses.

DR. A. B. BAKER: Let me first take up the question of retinal arteriosclerosis, which is very important. One must keep in mind that we are actually dealing with 3 sets of vessels within the human brain. First, there are the smallest vessels, the arterioles, under 150 μ. When these vessels undergo degenerative change, there is strictly a medial fibrosis which is quite different from the changes that we have been talking about. Then, there is a second set of vessels, the larger intracerebral vessels from 600 to 150 μ, which supply most of the brain. When these vessels undergo degenerative change, there is a proliferation of the adventitia which invades inward and finally replaces the entire vessel wall.

And, third, there are the larger vessels along the base of the brain which undergo true atherosclerotic change, an intimal proliferation and an intimal change. Now, the reason I mention this is that, when one speaks of cerebrovascular disease, he must delineate that type of vessel he is talking about. It is obviously not correct to try to compare changes along the base of the brain in the large vessels with the retinal vessels which are much smaller, many of them arterioles. Therefore, one can only say as he looks at the retinal vessels that he can predict, perhaps, what may be happening to similar sized vessels in some other part of the body but not to the large vessels. Unfortunately, most of the studies done to date have compared the vessels along the base of the brain with the retinal vessels, and this is not a correct comparison. No study has yet been done comparing the arteries of the brain with similar sized arteries elsewhere in the body. This is important because the tissue changes in these vessels are different, and one can't compare medial fibrosis with a change which happens to be intimal. I can say offhand now that we can't tell from looking at the eye grounds what is the status of the large vessels along the base of the brain nor the medium-sized vessels within the brain. We can probably predict changes in similar arteriolar-sized vessels within the brain.

The first question regarding the relationship of cerebral atherosclerosis to the many factors mentioned, such as heredity, dietary habits, and so forth, I can't answer, primarily because we have not done this type of study. Unfortunately, most of our case histories are not detailed enough for us to tell about dietary habits and blood lipids and their relationship to cerebral atherosclerosis. That would require a very carefully planned study over a long period of time. Such information is not generally available in most autopsy records, so we had to use the general factor of body weight.

The relationship of cerebral atherosclerosis to clinical cerebral thrombosis is a very important one. These are probably two entirely different but related processes. In cerebral atherosclerosis, we deal with a change in the intima, and I am convinced that this is a basic process. I have never seen a thrombosis without cerebral atherosclerosis. When a thrombus forms in the vessel, it is usually on an area of intimal atherosclerosis, no matter how small. But what process actually causes a thrombus to form on a single plaque within the entire circle of Willis in one person, while another person can have the whole circle very severely sclerotic and no thrombus, I don't know. It may be significant that since we do not see cerebral thrombosis without arteriosclerosis, we won't have to worry about the process of cerebral thrombosis if we can solve the problem of atherosclerosis.

Finally, regarding malignancy and atherosclerosis, we took into account the age factor in our patients, and it is quite apparent that the fact that patients with malignancy may die earlier does not play a role. Regardless of the age factor, when one takes these cases decade by decade, there is still a marked difference between the atherosclerotic process in patients with malignancy and in those without. I am convinced that this may be one of the few factors which may give us a lead to the process and mechanisms behind atherosclerosis.

DR. SCHMIDT: Do you mean to imply that there may be atherolysis in cases of malignancy? Most of the time, malignancy is fatal within a relatively short period of time, and we would either have to assume a biologic difference before the development of malignancy or lysis of the atherosclerotic plaques.

DR. A. B. BAKER: I wish I could answer your question. The point is that we have found more atherosclerosis in the patients who do not have malignancy than in those that do, irrespective of age. I think it has been noticed by others that patients with malignancies seem to have less generalized atherosclerosis. This absence is striking in the brain. Certainly, the malignancy relationship is much more striking than the better accepted factor that overweight persons have hardening of the arteries. In our statistics, obesity does not seem to make a bit of difference as to the severity and frequency of atherosclerosis, at least in the brain.

DR. KETY: We have a question from Dr. Bull addressed to any member of the panel.

"Does any member of the panel think that spontaneous occlusion of the cervical portion of the internal carotid artery occurs without producing any symptoms?"

DR. KAPLAN: Yes, that happens many times. In fact, we will sometimes occlude the artery surgically without any difficulty. Other times, of course, one gets trouble. Sometimes, the artery is occluded, and the patient goes along for one or two weeks and then becomes hemiplegic. Certainly, there can be an occlusion of the internal carotid artery in the cervical portion without any clinical findings.

DR. A. B. BAKER: I agree with Dr. Kaplan that there can be occlusion of the cervical portion of the internal carotid without clinical symptoms. We must remember, however, that our ability to evaluate subtle changes in brain function is extremely limited, and anything we evaluate is really very gross. I don't think any one knows whether one can get occlusion without anything happening clinically to the brain except within the range of our rough method of measuring brain function.

DR. BERRY: It is possible, however, to have an occlusion, either surgical or atheromatous, without any microscopic evidence of softening in the brain.

DR. KETY: Now we may ask Dr. Sokoloff to comment upon the discussion of his paper. I wonder whether he would take this opportunity to dwell a little further upon the relationship between the aging process and the cerebral circulation.

DR. SOKOLOFF: First of all, I would not like to create an impression, indicated by Dr.

Kety's remark, that the nitrous oxide method and its modifications need redemption. They all succeed in doing what they were designed to do—measure the average rate of blood flow through the brain taken as a whole. The point that I was trying to make is that the clinical aspects of cerebrovascular disease are more related to local blood flow phenomena, for which these methods were not designed. I am happy to see that progress is being made, as indicated by Dr. Ingvar's talk, toward a method which will permit the measurement of local blood flow, perhaps in man.

Dr. Lassen brought out what appears to be a point of difference between us and concerns the same point that Dr. Kety raised about the relationship between blood flow and oxygen consumption and oxygen tension in reference to the problems of aging. There is no doubt that, in the average elderly person, cerebral blood flow and cerebral oxygen consumption are reduced. There has been a question for a considerable period of time about which came first. Is there a reduction, first, in cerebral blood flow as a result, perhaps, of vascular disease changes, with a secondary reduction in cerebral oxygen consumption because of tissue ischemia, or, conversely, is there first a reduction in cerebral oxygen consumption because of parenchymatous changes, with a secondary adjustment of the cerebral blood flow to reduced cerebral metabolic rate? We have recently done some studies in a rather large group of what we hope are normal elderly persons, as free of vascular disease as we could find and functioning normally in their communities. All of these were about 65 years of age. In a highly selected portion of these subjects, those who were as free of evidence of vascular or any other kind of disease as we could expect to find in this age group, we found no change in cerebral blood flow or oxygen consumption below the levels of a control group fifty years younger. We also had, in addition, a smaller group which we hope was very much like the first. We found objective evidence of arteriosclerosis in these patients, so that they didn't fit the qualifications for the first group, although they were asymptomatic. In this group, we found a reduction in cerebral blood flow with no significant change in cerebral oxygen consumption, but there was a reduction in the oxygen tension of the cerebral venous blood. This probably reflects the oxygen tension in the cerebral tissues, suggesting that there was a reduction of blood flow first before any evidence of reduced metabolic rate in this group. Blood flow in these individuals was as low as that which we found in patients with chronic brain syndrome who were hospitalized for psychosis. The difference between the arteriosclerotic and the brain syndrome patients was that, in the latter group, low oxygen consumption was decreased proportionately to the decrease in blood flow. We believe that this arteriosclerotic group may represent a transition group in which there was first a reduction in blood flow. The only difference between the two groups was in the evidence of arteriosclerosis, so we attribute the reduction of the blood flow to it. The reduced oxygen tension was thus the result of reduced blood flow. We speculate that, after a prolonged period of reduced oxygen tension because of reduced blood flow, one might expect damage to the brain resulting in a reduced oxygen consumption and then development of symptomatology.

DR. LASSEN: It is very difficult to make from cerebral venous oxygen measurements a reliable inference as to the cortical oxygen tension. Furthermore, you cannot take only a reduction in venous oxygen tension and then imply a cortical ischemia or hypoxia, since you must also know the critical level which man can tolerate. As we all know, patients with chronic arterial hypoxia from lung disease may exist very well without any cerebral damage.

I want once more to say that I think this issue is open and should remain open until more evidence is accumulated.

DR. SCHEINBERG: I have been asked, "Is it true that cerebral blood flow is lowered by carotid ligation and unchanged by carotid or cerebral thrombosis?"

This has been touched upon in the previous discussion. There is considerable clinical evidence that this may happen. From the experimental point of view, evidence has been accumulated which indicates that cerebral thrombosis certainly may occur without change in cerebral blood flow. Several patients have been reported with an actual thrombosis of the carotid artery in whom there was no evidence

of reduction of cerebral blood flow. This was mentioned by Dr. Sokoloff. On the other hand, although the studies have been somewhat limited, acute occlusion of the carotid artery has resulted in a very striking reduction in cerebral blood flow and cerebral oxygen consumption. The obvious conclusion that one might draw from this is that gradual occlusion of a major cerebral vessel may result in sufficient collateral circulation to maintain blood flow to the hemisphere. Whether or not this is the total explanation, it seems to be a possible reason for such a situation. I think that Dr. Henry Shenkin has also demonstrated that ligation of a carotid artery results in a decrease in the arterial pressure peripheral to the ligation. If this reduction in arterial pressure is sufficient, thrombosis may occasionally result.

The second question is, "Do you still use 5% carbon dioxide and 95% oxygen inhalation in patients with cerebral infarct? Wouldn't that percentage of oxygen decrease cerebral blood flow?"

This is like asking somebody when he stopped beating his wife. The fact is that I do not use such a procedure in the treatment of cerebral thrombosis, although, as I indicated before, from the experimental point of view, this is certainly a device for increasing cerebral circulation. It happens that the presence of 5% carbon dioxide, even with 95% oxygen, results in a very striking cerebral vasodilation. The presence of the high oxygen tension does not vitiate against this effect.

DR. KETY: There is a question from Dr. Feindel addressed to Dr. Sokoloff.

"Is the large increase in cerebral blood flow associated with increased carbon dioxide tension due solely to vasodilation of the cerebral arterial vessels, or are other phenomena, such as vascular shunting, possibly involved?"

DR. SOKOLOFF: In most of the studies in which 5 to 7% concentrations of carbon dioxide have been used to study cerebral blood flow, there usually is an associated increase in arterial blood pressure but not enough to account for the marked increase in cerebral blood flow. At lower concentrations, studies by Patterson and his associates, using, I believe, down to 2.5 to 3.5% carbon dioxide, demonstrated an increase in cerebral blood flow—not as great as was achieved with the 5 to 7% but a definite increase, without any significant change in arterial blood pressure. As far as the shunting effect is concerned, the kind of shunting that would produce that degree of change (measured with the nitrous oxide method) would have to be arterial-venous shunting. As far as I know, there has been no satisfactory demonstration of A-V shunts in the brain.

DR. SCHEINBERG: Dr. Sokoloff, hasn't it also been demonstrated that a piece of carotid artery perfused with carbon dioxide or, actually, a dissected carotid artery perfused with carbon dioxide in solution will show dilation?

DR. SOKOLOFF: A number of studies have been made to get at the mechanism by which carbon dioxide dilates the cerebral vessels. There are several by Wolff and his associates in which all kinds of interruptions in nervous pathways did not eliminate the carbon dioxide effect. Then there is an observation at the early part of the century by Gow, who took isolated strips of the carotid artery, as Dr. Scheinberg said, and found that carbon dioxide in solution would dilate them, indicating that carbon dioxide has a direct effect on the smooth muscle of the cerebral arteries.

DR. KETY: May I comment upon the question of shunts? I do not believe that there is anatomic or physiologic evidence for shunts, true arterial-venous shunts, normally, in the cerebral circulation. With regard to the effects of carbon dioxide, although the nitrous oxide technic would not distinguish between shunts and capillary circulation, a number of the methods for measuring local blood flow, such as that with radioactive gas that Dr. Sokoloff mentioned and that which Dr. Meyer and Dr. Ingvar have been using, have been applied to the effects of carbon dioxide. All of these, which are not sensitive to shunt blood flow, show that carbon dioxide produces a true vasodilation and increase in capillary blood flow.

DR. MEYER: I want to thank my discussers. I think Dr. Stehbens has shown the biophysics behind turbulence. I do think that turbulent flow can be seen in the small cerebral vessels after occlusion, particularly if you inject methylene blue or trypan blue, using essentially the same technic that he has used in his glass model. I do believe it is of physiologic significance in hemodynamics because Ponder,

in England, about 1920, pointed out that adherence of red cells, rouleaux formation and aggregation, was in part dependent upon the number of times that the red cells collided. With turbulent flow, the liability for red cell collision is, I think, much increased.

I want to congratulate Dr. Ingvar on his great technical contribution to these problems of measurement of local blood flow. His absolute local blood flow method is a distinct advance, particularly if it proves to be thoroughly reliable. There are disadvantages of which I am sure he is aware. It is not a method of recording continuous absolute changes in blood flow, and, therefore, one has to sample. This is one of the objections that was mentioned early in the discussion. The ideal method of measuring local blood flow, or any other type of cerebral blood flow, would be continuous. Hence, we have used qualitative thermistor technics. These are similar to thermocouple measurements except that these electrodes do not require heating and cooling, are very sensitive, and record quite satisfactorily with the polygraph.

Dr. Kaplan made a reference to the changes in blood flow with increased intracranial pressure, and I would like to refer to the work of Harvey Cushing at the turn of the century. He pointed out that, when one increases intracranial pressure, one doesn't significantly alter hemodynamics until the intracranial pressure exceeds the mean arterial blood pressure. There is the compensatory rise of the so-called Cushing phenomenon in which the blood pressure tends to rise to preserve the medullary centers from ischemia. However, with cerebral infarction, anoxia from nitrogen breathing, and other causes of acute brain edema, we have definitely seen compression of cerebral vessels due to edema rather than to pure increase in intracranial pressure through microscopic and photographic records of cerebral vessels through windows in the skull. I would tend to agree that it is the swelling of the brain that is important rather than the simple increase in cerebrospinal fluid pressure.

DR. KETY: I think a case can still be made for a rather straightforward hemodynamic and hydraulic relationship between intracranial pressure and cerebrovascular resistance. In the studies which we did with Shenkin ten years ago, a linear correlation was demonstrable between intracranial pressure and cerebrovascular resistance. Harvey Cushing's studies were related more to physiologic symptomatology than to hemodynamics, and, although it is true that a severe embarrassment of cerebral circulation may not occur in a linear manner with increased intracranial pressure, this is the result of a number of compensatory mechanisms. But cerebrovascular resistance, as Starling's theory and straightforward hydraulic theory would predict, does increase pari passu with intracranial pressure. It is the operation of these compensatory reflexes which maintains the cerebral circulation in the face of these mechanical effects.

Dr. Stehbens, there are two questions which have been addressed to you.

The first is whether you would comment upon the frequently observed phenomenon that radiopaque material injected into one vertebral usually elucidates the corresponding posterior fossa, suggesting a laminar type of flow in the basilar artery.

The second question is "What effect will changes in the elasticity of arteries have on the development of turbulence?"

DR. STEHBENS: I think that vertebral angiography isn't really going to help you display laminar or turbulent flow, as it is a rather slow process. I believe that MacDonald in 1952 showed that turbulence did occur in the rabbit aorta, which has a diameter of about 3 to 4 mm. Although today high-speed cinematography is used, I am not really sure that one can display turbulent flow by the rather slow exposure of roentgen angiography.

As for the second question, as man increases in age, the elasticity of his arteries is diminished. He has extensive destruction of elastic tissue within the vessel wall progressively throughout life, but I think he also has some proliferation of elastic tissue. The hardening of the vessel wall which is associated with the changes in the elasticity, or at least elastic tissue, occurs simultaneously with the many other changes, not only the changes in the lipid but also those in the calcium content of the vessel. The hardening of the vessel wall may considerably alter the hemodynamics, a circumstance which possibly explains the increase in systolic pressure that occurs during

life. Whether the increase in systolic pressure alters the velocity of flow, I wouldn't like to say, but it is possible that the increase in systolic pressure increases the damage to the vessel wall. Other than that, I don't think at the present time you can say what effect elasticity is going to have on turbulent flow.

DR. BERRY: Dr. Stehbens, perhaps you or Dr. vander Eecken can tell me about the differences in animal circles of Willis. Animals frequently don't get arteriosclerosis. Is there some anatomic difference in the angularity of the vessels in the lower animals that would be of significance?

DR. STEHBENS: The business of other animals having cerebral arteriosclerosis is rather difficult. First of all, veterinary surgeons are not really interested in cerebral arterial disease or other arterial disease. They are only interested in diseases which pertain to domestic animals and herds. When you compare arterial disease in man to arterial disease in other animals, the age of the animal is another factor which I don't think has been considered. Most of the animals we use frequently only live a short while, probably because they are killed early. The size of the vessel is also important. The angle of branching in all animals, I think, varies considerably and its importance is doubtful. Dr. Baker demonstrated that the larger the vessel, the more likely is there to be a severe degree of atherosclerosis. I think that it is both age and the size of a vessel rather than the angle of bifurcation which are significant in comparing animals.

DR. INGVAR: Dr. Meyer brought up a question about our method being a sampling method and not a continuous one for measuring local cerebral blood flow. Of course, I agree. But, on the other hand, with our technic, we are following the clearance of the radioisotope, krypton 85, for about three minutes. During this time, it is possible to make different experiments upon the cerebral circulation, study their effect upon the clearance curve, and then compare them with a clearance curve under control conditions. In this way, we have studied the effects of epileptic seizures and of changes of the systemic circulation, and we have some preliminary results. There is also the possibility of using the krypton method in combination with a continuous method of the type used by Dr. Meyer, a thermoelectric method. However, there are at the moment rather complex theoretic questions involved in a combination of two such methods, and I am afraid I will have to abstain from any further comments.

DR. KETY: One interesting concept which has emerged from the recent studies of the physiology of the cerebral circulation is that of the importance of intrinsic control, the remarkable homeostatic mechanisms by which the brain as a whole and the functioning nuclei of the brain modulate the flow of blood to them in relationship to their metabolic needs. This, in a way, was a drastic revision of the earlier ideas of the physiology of the cerebral circulation which persisted in many of the textbooks until quite recent times—the concepts that the cerebral circulation passively followed the blood pressure and that rises and falls in the blood pressure were immediately and irrevocably associated with corresponding changes in cerebral blood flow. Actually, those erroneous concepts came largely as the result of Leonard Hill, whose rather vague experiments, coupled with very dogmatic conclusions, dominated the concepts of cerebral circulation for a long generation. Interestingly enough, however, these modern concepts of which we heard so much today from Dr. Sokoloff, Dr. Meyer, and their discussants actually had an earlier basis in the writings of none other than Sherrington. In 1890, a very interesting paper by Roy and Sherrington upon the cerebral circulation appeared in the *Journal of Physiology*. Using very inadequate methods, but very astute reasoning, these workers came to the conclusion that an important control of the cerebral circulation was not in the arterial blood pressure but in the intrinsic metabolism of the brain. They even suggested that the mechanism whereby the local metabolism was met by a corresponding change in local blood flow was by way of carbon dioxide tension of the cerebral tissues immediately adjacent to these areas of metabolism and blood flow. Thus, we see that we have come, in a way, in a circle and that these modern concepts of the physiology and control of the cerebral circulation were foreshadowed by the work of one of the great leaders in experimental neurology.

Use and limitations of angiography in the diagnosis of vascular lesions of the brain

James W. D. Bull, M.D.

ANGIOGRAPHY GIVES accurate results in the diagnosis of aneurysms. We reviewed[1] the records of 210 of our patients with subarachnoid hemorrhage, all of whom had had cerebral angiography and were shown at autopsy to have ruptured aneurysms. During life, 89% were diagnosed correctly angiographically. The causes of error in the remaining 11% were analyzed, and the conclusion was reached that the potential accuracy of radiologic diagnosis was approximately 96%. The most important point in technic is the taking of multiple projections. Besides the conventional lateral and anteroposterior views, supplementary oblique, reverse oblique, and periorbital anteroposterior projections are often necessary.

The standard of accuracy in the diagnosis of arteriovenous malformations (angiomas) is much more difficult to assess, because the incidence and the mortality rate, and thus autopsy figures, are far lower than in the case of ruptured aneurysms. That the accuracy is high for the most part can be assumed, but I have little doubt that angiography fails to demonstrate very small angiomas.

In diagnosing the cause of a stroke, angiography is far less accurate. Over the last two years, Marshall and I and our colleagues have been investigating an unselected series of acute strokes, one of the objects being to evaluate the usefulness of angiography.

The first problem was to define a stroke, which is not easy. We made the following definition of an individual with stroke: "A patient who, on clinical evidence, has sustained a cerebrovascular accident (including the great vessels of the neck) *not* due to an aneurysm or arteriovenous malformation." In practice, this definition soon breaks down, since aneurysms, arteriovenous malformations, and tumors may first manifest themselves with a stroke.

Fig. 1. Cast of arteries of brain made by Dr. D. H. Tompsett

ANATOMY

Angiography performed during life is a crude procedure when compared with good autopsy casts and radiographs thereof. Figure 1 is a lateral photograph of a cast; Figure 2, a radiograph of the same cast; and Figure 3, a good quality carotid angiogram taken during life. As is obvious from these illustrations, much detail is lost at angiography, not only because the contrast substance probably permeates the very small vessels better in death than in life, as more time and greater pressure are permitted for filling the vessels, but also because radiology has certain inherent

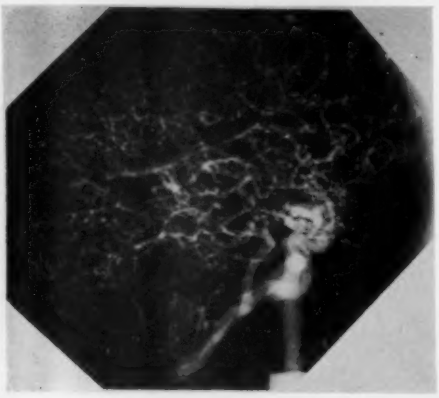

Fig. 2. Radiograph of cast in Figure 1

deficiencies. I refer to such factors as radiation scatter, which cannot be eliminated entirely, the size of the grain of x-ray films and intensifying screens, and the size of the focal spot of the x-ray tube. These factors, together with possible slight movements of the patient's head, the x-ray apparatus, or both, tend to diminish detail on the radiograph.

MATERIAL

We performed angiograms—78 carotid and 2 vertebral—on 80 consecutive patients. We diminish detail on the radiograph.

trauma and confined ourselves to the injection of only one cerebral vessel. This we sometimes found to be hampering from the diagnostic point of view. For the same reason, we avoided making vertebral angiograms as much as possible, as, rightly or wrongly, we thought the morbidity rate might be greater. Table 1 shows the clinical diagnosis on admission, together with the initial angiographic findings. Table 2 shows the angiographic breakdown. In a few cases, the clinical condition progressed, making further angiographic examination necessary; in one case, 3 angiograms were performed over a period of about two

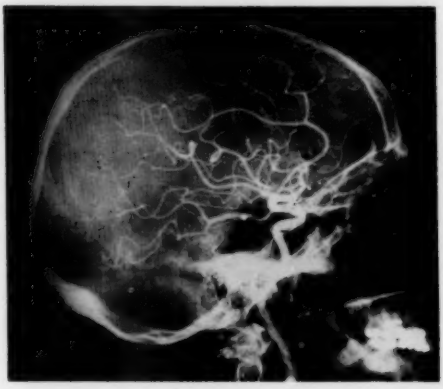

Fig. 3. Normal lateral arteriogram taken during life

TABLE 1

INITIAL CLINICAL AND ANGIOGRAPHIC DIAGNOSES

Clinical diagnoses on admission	*Number of clinical diagnoses*	*Angiographic diagnoses*							
		Normal	*Middle cerebral occlusion*	*Anterior cerebral occlusion*	*Internal carotid occlusion*	*Basilar occlusion*	*Intracerebral hemorrhage*	*Aneurysm*	*Failed angiogram*
Middle cerebral occlusion	41	29	3*		6		3		
Anterior cerebral occlusion	4	2		2*					
Internal carotid occlusion	11	6	1		4*				
Basilar occlusion	4	1				2*			1
Intracerebral hemorrhage	15	7	2		2		3*	1	
Middle cerebral embolus	5	1	2*		2				
TOTALS	80	46	8	2	14	2	6	1	1

*Angiographic diagnosis supported clinical impression

years. Table 2 shows the *final* angiographic analysis.

Various points emerged: [1] The angiograms were grossly abnormal in 32 patients, or 40%, and the internal carotid artery was pathologically narrow near its origin in 4 other patients. [2] Middle cerebral occlusion was the most common clinical diagnosis and was the second most common angiographic finding, the most common being carotid occlusion. [3] The clinical diagnosis was often upset by the angiographic findings. [4] The clinicians usually found themselves unable to differentiate middle cerebral from internal carotid arterial occlusion before angiography.

TABLE 2
FINAL ANGIOGRAPHIC ANALYSIS OF STROKES

No abnormality detected		
Carotid	42	44
Vertebral	1	
Vertebral failed	1	
Slight abnormality detected		
Slight stenosis of internal carotid	4	
Gross abnormalities		
Internal carotid occlusion	10	
Middle cerebral occlusion	8	
Intracerebral hemorrhage*	8	
Anterior cerebral occlusion	2	
Basilar occlusion or insufficiency	2	
Anterior and middle cerebral occlusions	1	
Tumor	1	
TOTAL	80	

*One hemorrhage secondary to aneurysm; both demonstrated angiographically

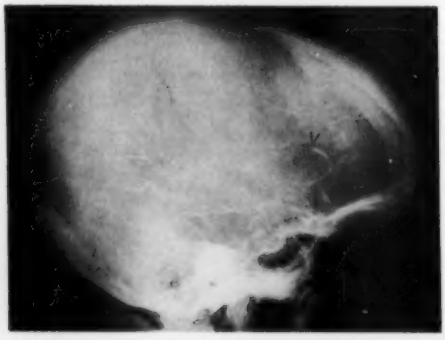

Fig. 4. Late arterial phase. Note obstruction (V) to flow of contrast substance in anterior cerebral artery

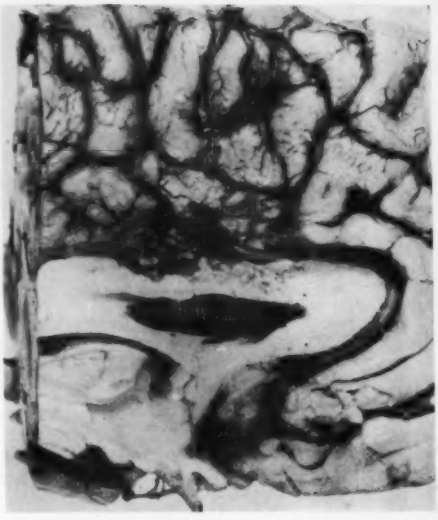

Fig. 5. Autopsy confirmation. Note infarcted zone in corpus callosum. (Courtesy of Prof. W. Blackwood)

POSITIVE ANGIOGRAPHIC FINDINGS

Only gross lesions were included in this group. Minor changes, which may be arguable, will be mentioned later.

Complete or partial occlusion of the internal carotid artery is easily shown, and the appearances are well known. Middle cerebral arterial occlusion occurs classically about 1 cm. from the origin of the vessel and just proximal to its bifurcation or trifurcation. Angiographic diagnosis of more distal middle cerebral artery occlusion is difficult, as the number of main branches arising from the middle cerebral artery varies. Hence, the absence of a vessel shadow does not necessarily indicate occlusion but perhaps may merely indicate congenital absence.

Occlusion of the anterior cerebral artery was only diagnosed when the lesion was situated

Fig. 6. Phlebogram showing cerebral edema

distal to the anterior communicating artery (Figs. 4 and 5). Owing to the anomalies of the anterior part of the circle of Willis, a diagnosis of proximal anterior cerebral arterial occlusion is not permissible unless bilateral carotid angiography is performed, and even then it may be difficult, since, in rare instances, only one main vessel trunk is present. Similarly, occlusion of the posterior cerebral artery should only be diagnosed after both carotid and vertebral angiograms have been made, as the posterior cerebral artery fills sometimes from one main trunk and sometimes from the other. Basilar occlusion was twice diagnosed in the series by carotid angiography on the basis of the reflux filling of this vessel from the posterior communicating artery. Absolute confirmation would have required vertebral angiography in addition.

SPACE-OCCUPYING MASSES

Strictly speaking, hemorrhage cannot be differentiated angiographically from edema or indeed any other avascular space-occupying mass, since the diagnosis is made on vessel displacement. However, if a major vessel, such as the main trunk of the middle cerebral artery, is occluded in association with a displaced anterior cerebral artery and/or midline veins, edema can be confidently diagnosed (Figs. 6 and 7). Temporal hematomas are more easily localized angiographically than are those in other situations.

Tumors are diagnosed by noting displacement of the main vessels and pathologic circulation. Such a case—a grade 3 astrocytoma—was diagnosed in the series. In this patient, the first arteriogram was negative. Deterioration of the patient's condition prompted us to repeat the examination seven weeks later, by which time the tumor mass and its pathologic circulation had become apparent. Reexamination of the first angiogram revealed no abnormality.

Another tumor was noted in the series some months after angiography. At biopsy, after ventriculography, cerebral metastases were seen. The angiogram was normal, even when examined retrospectively. Presumably, the metastases were too small to be shown at the time of angiography.

If the angiogram shows a wideswept anterior cerebral artery lying in the midline, a hemorrhage or other mass in the midbrain or posterior fossa should be suspected. Vertebral angiography often shows a normal vascular tree. Pneumography should then be done. If a mass is present in the midbrain or posterior fossa, it will almost certainly be revealed, provided that the air is properly manipulated into the posterior end of the third ventricle, the aqueduct, and the fourth ventricle. If adequate

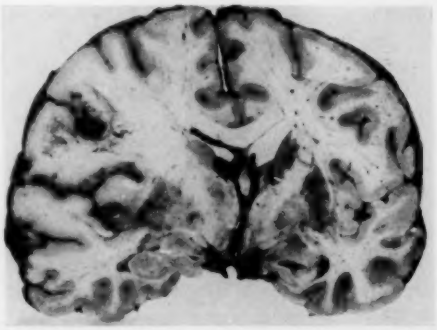

Fig. 7. Autopsy of case in Figure 6. Edema is clearly shown. (Courtesy of Prof. W. Blackwood)

filling is not obtained, positive contrast ventriculography should be performed.

These cases—midbrain and posterior fossa hemorrhages—demonstrate the importance of bearing in mind radiologic procedures other than angiography in the investigation of strokes. It should be noted that a normal sweep of the anterior cerebral artery does *not* exclude a midbrain or posterior fossa hematoma or other mass.

All lesions so far described were gross. In over half of our 80 cases, no abnormality was detected on the angiogram. Autopsy revealed 7 cases of intracerebral hemorrhage that had not been shown angiographically (Fig. 8); 4 cases of hemorrhage shown at angiography were confirmed at autopsy. It can be argued that the hemorrhages which were not revealed angiographically had become larger and more obvious at the time of autopsy. This may be true, but some hematomas, even of moderate size, cannot be diagnosed on the angiogram. If a hemorrhage is suspected despite the normal angiogram, pneumography should be done. My experiences with my surgical colleagues, Mr. McKissock and Mr. Walsh, outside Marshall's series are that sometimes the pneumograms are also normal, even in the presence of a sizable hematoma.

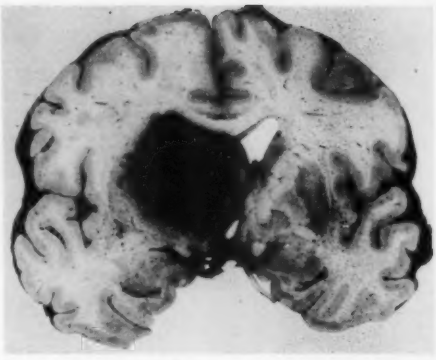

Fig. 8. Normal carotid angiogram. Autopsy showed a massive intracerebral hemorrhage. (Courtesy of Prof. W. Blackwood)

ATHEROSCLEROSIS

It might be thought that, by analogy with the great vessels such as the aorta, one could recognize atherosclerosis radiologically by observing increased tortuosity, variations in caliber of an artery or arteries, and local irregularities in the walls. We have studied these features objectively[3] and found no correlation between incidence of tortuosity and the known presence of cerebrovascular disease. However, in the case of caliber variation and local irregularities in the walls, such a positive correlation did exist, although, of course, these features were not confined solely to the stroke cases and were seen to a lesser extent in control subjects of the same age. Thus, in isolation, they cannot be taken as diagnostic criteria.

For purposes of the present analysis, we have considered as abnormal only those cases in which the origin of the internal carotid artery was obviously stenosed. There were 4 such cases in the series.

THORACIC PORTION OF THE GREAT VESSELS

In consideration of the pathology of strokes, there is now a greater awareness of the importance of the thoracic and cervical portions of the arteries supplying the brain.[4] In order to outline the origins of the common carotid and vertebral arteries, a technic different from the conventional one must be used. Various methods have been tried, but, as far as I am aware, none has as yet proved entirely satisfactory.

Catheterization of certain arteries has been advocated. In my opinion, all these technics have their disadvantages. Femoral percutaneous catheterization with retrograde threading of the catheter up to the aortic arch would appear to be a sound procedure. In practice, however, it is often difficult to achieve, as most patients are elderly and their iliac arteries tend to be tortuous and rigid. As a result, it is sometimes impossible to pass the catheter.

Retrograde percutaneous subclavian puncture is an admirable method for outlining the origin of one vertebral artery, but, since visualization of the origin of both vertebral arteries is often desirable, bilateral puncture is necessary. The chief hazard is puncture of the pleura, with the precipitation of a pneumothorax, the risk being about 10%.

We are hopeful that the method of Viallet and his colleagues[5] may be more successful and less dangerous. Their technic consists of rapid intravenous injection of a large quantity

of a concentrated contrast medium. They found that, particularly in children, the arterial tree of the whole body could be outlined.

The great advantage of this method is that the mouths of all four major arteries supplying the brain are seen simultaneously at one injection. Another advantage of venous injection is that there is no danger of damaging any artery in a patient who almost certainly suffers to a greater or lesser degree from atherosclerosis. Probably the best technic is to inject the contrast substance into each antecubital vein simultaneously. By this means, the two boluses reach the right heart more or less together and probably a greater concentration takes place in the aorta. We have only recently begun to use the method and have found that timing of the radiographic exposures and careful positioning of the patient are essential.

In conclusion, I think one should aim at developing an intravenous technic, with the object of opacifying the whole of all the cerebral arterial trees from the upper thorax to the cranial vertex, preferably in at least two planes. A bland contrast substance, two or more injections of which could be safely given, would be required. This procedure could be regarded as survey angiography. Depending on the findings, it might be necessary to proceed afterward to a more detailed angiographic examination of one of the main vessels. This procedure would be performed by arterial puncture in the current conventional manner.

The author is grateful to his colleague, Professor Blackwood, for Figures 5, 7, and 8 and to Dr. D. H. Tompsett for Figure 1.

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Angiographic observation in occlusive cerebrovascular disease

Juan M. Taveras, M.D.

ANGIOGRAPHIC DIAGNOSIS of occlusion of the internal carotid artery in its cervical or intracranial portions and of the vertebral and basilar arteries, as well as occlusion of the trunk of the middle cerebral artery, is relatively simple. It is more difficult to ascertain the presence of occlusion of distal branches of the middle, anterior, or posterior cerebral vessels.

Occlusion of distal branches of the middle cerebral artery may be suspected when a paucity of vessels in one given area is an isolated finding. Unfortunately, anatomic variations are common, and sometimes one cannot tell whether occlusion of a given vessel or a simple anatomic variant is present.

By studying the collateral circulation on the surface of the brain, it is possible to diagnose with certainty, in some cases, obstruction of distal branches of the main cerebral arteries. Seriograms are indispensable to the study of collateral circulation.

It is now a well-known anatomic fact that there are direct end-to-end anastomoses between branches of the anterior, middle, and posterior cerebral arteries on the surface of the brain—the so-called meningeal arterial anastomoses. Blood flow in the middle cerebral branches in the central portion of the convexity of the brain is upward and backward. The flow in the anterior cerebral branches is also upward and backward but is downward after the blood reaches the uppermost portion of the medial surface of the hemisphere. Many branches of the anterior and middle cerebral arteries undergo direct end-to-end anastomoses; therefore, at some point in these arteries, equalization of blood pressure should result in very little flow. In the case of the middle and anterior cerebral artery branches, this zone is probably near the highest point along the superior margin of the hemisphere. Within the major anastomosing vessel, the flow at this point is probably strictly toward the perforating branches supplying the brain.

If the pressure on one side of the system is lowered while the other side remains open, the blood flow will be reversed and the branches will fill from a direction opposite to the usual. This observation makes possible diagnosis of complete, and suspicion of partial, thrombosis of branches of the middle, posterior, and anterior cerebral arteries.

In cases of middle cerebral thrombosis, the collateral circulation is usually by way of the branches of the anterior, and sometimes of the posterior, cerebral artery (Fig. 1); at other times, both arteries contribute to the collateral supply. In one case of thrombosis of the distal portion of the posterior cerebral artery, the supply came from branches of the middle cerebral artery (Fig. 2). In a case of thrombosis of both pericallosal arteries, the collateral supply originated from the posterior cerebral arteries (Fig. 3).

Arterial and arteriovenous circulation times are increased in patients with thromboses. Proportionately, the time from beginning of arterial filling to arterial emptying is increased more than the time from maximum concentration of contrast substance in the carotid siphon to that in the parietal veins. Usually, the contrast substance is still visible in the collaterals when it has disappeared from the other arterial channels (Figs. 1 and 2). The collateral circulation time, measured as the time from appearance to disappearance of collateral channels, is from two to six seconds. Over four seconds is considered dangerously slow. Some of our patients had what was considered to be definite *stasis* of the contrast substance in the

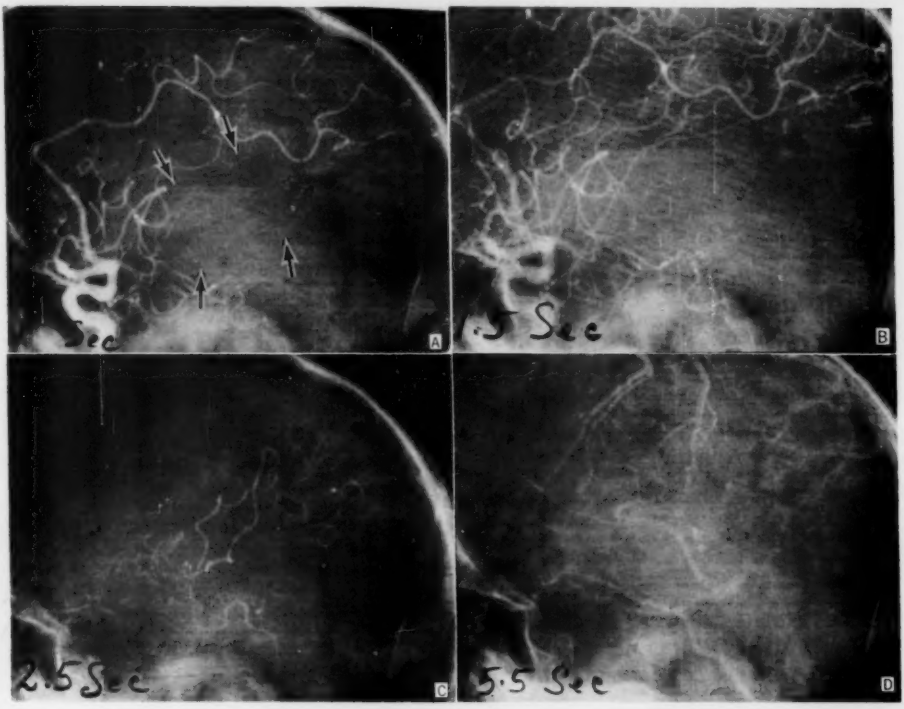

Fig. 1. Obstruction of some branches of middle cerebral artery, with collateral circulation from anterior cerebral. A and B represent arterial phase, showing lack of filling in posterior portion of middle cerebral territory. A clear area devoid of major arterial branches is seen in area indicated by arrows. C is a film made at two-and-a-half seconds, in which all arterial channels previously filled have emptied and only area previously unfilled stands out. Since there was no posterior cerebral artery filling, filling obviously took place by retrograde flow from anterior cerebral branches. Arterial circulation time, including time in collaterals, was three seconds, which is moderately above average. At five-and-a-half seconds [D], all arteries have emptied and veins have reached maximum filling. Arteriovenous circulation time was between five and five-and-a-half seconds, which is also moderately above mean arteriovenous circulation time in adults.

collateral channels, and narrowing of the collateral channels was also present in some cases. Stasis in the collaterals was considered to be an indication of possible propagation of thrombus or of partial thrombosis, which impeded the normal flow, or was due to parenchymal changes in the brain that resulted in capillary block, thus causing the contrast substance to remain in the arteries.

The possible prognostic value of the collateral circulation as demonstrated angiographically on initial examination is being investigated, but as yet no conclusions can be reached. We are more interested in the immediate than we are in the long-term prognosis, which is dependent upon a great many other factors.

How long do surface collaterals take to develop in the brain? Probably a very short time, or no time at all. A difference in pressure to cause reversal of flow is all that is needed. On the other hand, collateral flow from the external to the internal carotid artery may take time to develop.

Spasm, that is, diffuse narrowing of vessels as seen angiographically, has not been as frequent a finding with thrombosis of intracranial vessels as with ruptured intracranial aneurysms. Several patients with spasm presented an abrupt onset that suggested a ruptured aneurysm, but the angiogram revealed an inter-

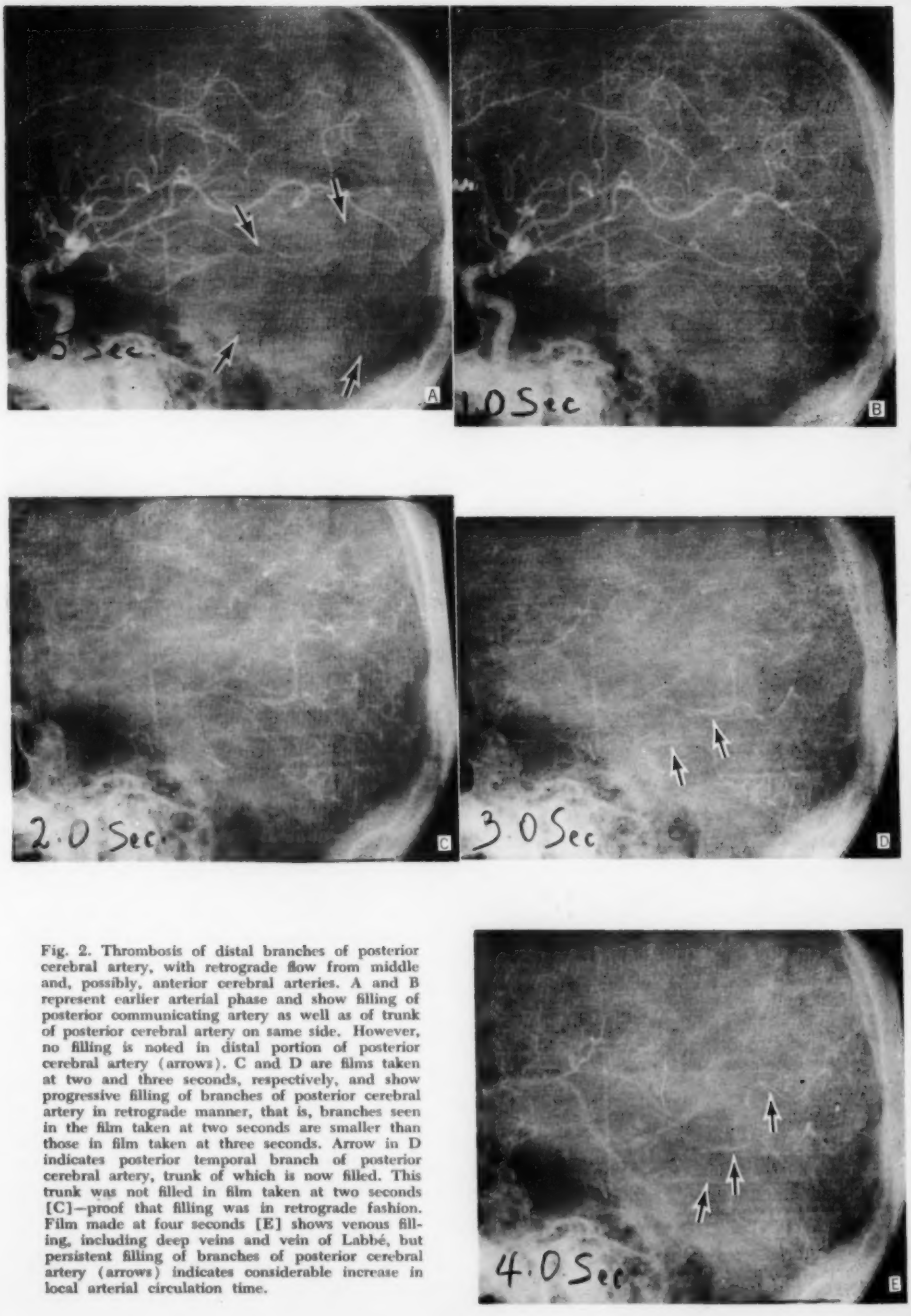

Fig. 2. Thrombosis of distal branches of posterior cerebral artery, with retrograde flow from middle and, possibly, anterior cerebral arteries. A and B represent earlier arterial phase and show filling of posterior communicating artery as well as of trunk of posterior cerebral artery on same side. However, no filling is noted in distal portion of posterior cerebral artery (arrows). C and D are films taken at two and three seconds, respectively, and show progressive filling of branches of posterior cerebral artery in retrograde manner, that is, branches seen in the film taken at two seconds are smaller than those in film taken at three seconds. Arrow in D indicates posterior temporal branch of posterior cerebral artery, trunk of which is now filled. This trunk was not filled in film taken at two seconds [C]—proof that filling was in retrograde fashion. Film made at four seconds [E] shows venous filling, including deep veins and vein of Labbé, but persistent filling of branches of posterior cerebral artery (arrows) indicates considerable increase in local arterial circulation time.

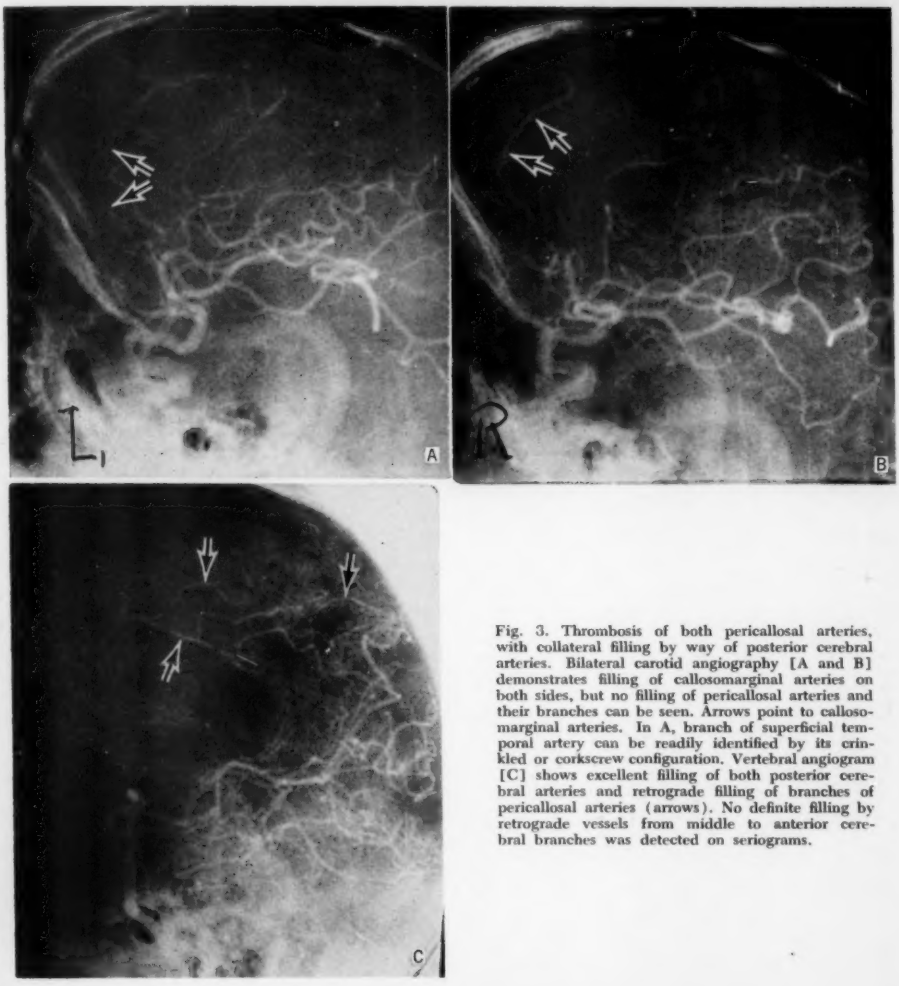

Fig. 3. Thrombosis of both pericallosal arteries, with collateral filling by way of posterior cerebral arteries. Bilateral carotid angiography [A and B] demonstrates filling of callosomarginal arteries on both sides, but no filling of pericallosal arteries and their branches can be seen. Arrows point to callosomarginal arteries. In A, branch of superficial temporal artery can be readily identified by its crinkled or corkscrew configuration. Vertebral angiogram [C] shows excellent filling of both posterior cerebral arteries and retrograde filling of branches of pericallosal arteries (arrows). No definite filling by retrograde vessels from middle to anterior cerebral branches was detected on seriograms.

ruption of the flow of contrast substance in the vessels, suggesting thrombosis; a few other patients had stasis and spasm in the collaterals. Aside from these cases, no instances of diffuse narrowing of vessels suggestive of spasm were seen. The absence of spasm in patients with bleeding aneurysms was noted in 27 of 31 patients aged 51 to 70 reported by Fletcher, Taveras, and Pool,[1] although 8 of them had had a recent bleeding episode. In 9 of the 31 patients, arteriosclerosis, as indicated by tortuosity, irregularity in contour, calcifications, and irregular narrowing and widening of the lumen, was present. On the other hand, in 35 of 69 patients under 50 years of age, spasm, as evidenced by diffuse narrowing of the vessels, was observed. It was the authors' impression that, when arteriosclerosis was present, the vessels did not become narrow, as is common with bleeding aneurysms. These findings seem to indicate that spasm may not be a factor in cerebrovascular disease in the older

age group. Spastic narrowing of a large vessel proximal to an obstruction is common but is due to the absent flow in that segment of the vessel.

CONCLUSIONS

1. Thrombosis of individual branches of the main cerebral arteries can be diagnosed by observation of filling of a given area through collateral channels. This cannot be accomplished without adequate serial films to record all phases of the cerebral circulation during angiography.

2. Extreme slowness of the circulation in the arterial channels filled by collateral flow may be local or generalized.

3. The arterial circulation time is usually increased with thrombosis.

4. Arterial spasm, as manifested by narrowing of arterial channels on cerebral angiography, is relatively uncommon.

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Discussion of "Use and Limitations of Angiography"

Oscar Sugar, M.D., Ph.D.

As Dr. Bull has pointed out, cerebral angiography is a somewhat gross diagnostic technic, but it is the best that we have at present. Of course, it does not show all the lesions in the vascular tree—in fact, it is not even reliable for all the aneurysms which may be disclosed at autopsy. On the other hand, the clinical diagnosis of stroke is notoriously erroneous. The large series of Riishede[1] and Gurdjian and his colleagues[2] with angiographic diagnosis make this evident. Many patients with strokes are apparently beyond hope of reversal of their neurologic deficit, but a certain percentage certainly can be helped by evacuation of a subdural hematoma, evacuation of an intracerebral hematoma from the temporal lobe (removal from the region of the basal ganglia does not seem to be very effective), or attack on a tumor or aneurysm, if such a lesion is found.

In this country, there appears to be no paucity of neurologic surgeons, yet I do not know where we would get enough to investigate all the cases of stroke. It may be that we, too, will some day come to the point of having angiograms done by the radiology department. There is good evidence, most recently presented in the Harvey Cushing Society meetings, that the incidence of complications with angiography diminishes with the increasing experience of the operator. The incidence of complications varies considerably, from none to 10%, depending on the criteria and reliability of the reporter. No doubt complications do occur, and if you have not encountered serious ones, consider yourself exceedingly lucky. If we are going to use angiography widely for diagnosis, we must decrease the complications by use of ever less toxic contrast materials, by decrease in time of anesthesia if this is used, by fewer punctures, and so forth.

Today, I would like to speak on the subject of anesthesia in angiography. In the past, I have used general anesthesia almost exclusively because of the reduction in seizures and because sometimes I can't find the arteries in the neck. However, I have been won over to the side of those using local anesthesia because of the recent availability of a new morphine analogue called phenazocine, which is commercially available as Prinadol (SKF 6574, NIH 7519). With this material given intravenously, the patients are quiet, sleep, stir not at all during injection of the contrast material, and recall virtually nothing of the procedure. At any time, the patient can be roused by being called and commanded to do a task—most often, to breathe, because considerable respiratory depression occurs in some patients, with resulting cyanosis. However, all one has to do is call out, "Mr. X, take a deep breath." The patient does so, and the cyanosis disappears. After each injection of dye, the patient can be asked to move or speak, so that, if a complication should arise, it can be noted immediately and proper treatment instituted. In a series of over 200 patients studied in cooperation with Dr. Max Sadove and his associates[3] in the Department of Anesthesiology at the University of Illinois and its associated hospitals, I have encountered transient hemiplegia only once—in a woman who had had a transient vascular ischemic episode. She became hemiplegic while the needle was in place in the artery but before the injection had been made. Cyanosis was marked. Procaine was injected intraarterially, oxygen was given under positive pressure, and, as soon as her color had become pink, her weakness

disappeared. With continued oxygen administration, subsequent injection of one dose of Hypaque was made without ill effects and disclosed no evident occlusive disease.

The initial Prinadol dose is usually 1 to 2 mg. intravenously, with 1- to 2-mg. doses thereafter until the patient is sedated. At any time, injection of the morphine antagonist, Lorfan (L-3 hydroxy-N-allylmorphinan tartrate), can nullify the respiratory depression, and actually, after 2 to 3 injections, if more sedation is needed, we sometimes mix the 2 drugs in the syringe and give the mixture.

In comparison with other commonly used narcotics, phenazocine produces less hypotension, which has always been a potent source of complications in my experience, and has a greater analgesic activity, a faster onset, and a longer duration of action. This drug is said to produce less respiratory depression than morphine or Demerol Hydrochloride when used intramuscularly but certainly depresses respiration when given intravenously. This material will, I am sure, help to diminish complications.

High brachial injection on the right and subclavian injection have their enthusiastic backers, and it seems that these technics may obviate local troubles such as spasm and local thrombosis. Very probably, these indirect injections should be used in patients with strokes.

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General discussion of angiography section, second session, May 1, 1960

Dr. Peritz Scheinberg, Chairman

DR. SCHEINBERG: I would like to begin by asking any of the original speakers whether they agree with Dr. Sugar's concept of the inherent danger of performing vertebral arteriography on patients with cerebrovascular disease and whether, in fact, it is advisable to look for an indirect method of doing this to avoid these dangers.

Dr. Bull, could you make any comments about that? Dr. Bull has been asked a number of questions about the complications of angiography which he might also comment upon.

DR. BULL: I do agree with Dr. Sugar that it would be very desirable to leave the vertebral artery alone and not traumatize it by puncture. One of my colleagues in London has demonstrated a considerable amount of trauma on the vessel wall with a mural thrombus in patients who have died following, but not as a result of, angiography. It is really remarkable that we don't get more complications in that way. The question is what indirect method to use. I personally don't like the idea of using the brachial artery because there have been recorded instances of loss of blood supply to the hand, and that, of course, is a very serious complication. I think the femoral artery is safer, but, in elderly persons, the iliac arteries are very tortuous because they are usually atherosclerotic and one may not be able to pass the catheter up to the arch of the aorta. I don't like retrograde puncture of the subclavian because of the complication of pneumothorax which occurs in about 10% of the cases, and you must do it bilaterally to show both vertebrals. So we are left with a method which I think was started by Villaret and his colleagues at the University of Algiers. They injected a large bolus of contrast media intravenously and obtained particularly good pan-angiograms of the whole body in children. We have just started using this method at Queen's Square, but we have not done enough cases to record any results. If you can get a large bolus into the vein, I think there is a good opportunity of showing the cervical portion of the vessels which we must consider more seriously than we have in the past and, perhaps, we will get a clear outline of the intracerebral vessels. We have been using both antecubital veins simultaneously, injecting about 40 cc. of 90% Hypaque. There are certain disadvantages, of course, because, particularly in the lateral view, both sides are superimposed and the interpretation will be more difficult, but it may be a good screening method. One may get a clue as to which vessel needs further analysis, and a percutaneous puncture of that vessel may be performed. I think that is the direction we should look in the near future.

The next question is, "What was the percentage of complications of angiography in Dr. Bull's series?"

In Dr. John Marshall's series of 80 cases, he and his assistants looked for complications very carefully and they found a 10% incidence. They were very strict in their criteria. If there was any deterioration in the condition of the patient, this was regarded as a complication of angiography. They found transient hemiplegia and aphasia. All of the patients with these complications reverted to their former state after one to three days. I think it is fair to say that angiography did not make any of them worse permanently. This question of complication rates, of course, is a frightfully difficult problem. I have had 2 patients who had fatal coronary thrombosis just before I intended to perform an angiogram on them,

and I am quite sure that if it had happened half an hour later I would have been blamed.

I would just like to make the point that I think that Thorotrast can be valuable in elderly patients, particularly if they are uncooperative. I don't think it is very popular in this country. We try to avoid using general anesthesia if we can, unless the patients are children or are in a state halfway between consciousness and unconsciousness, when they just won't cooperate, and try to pull the needle out even if you tie them down. They may move their heads when they get the sensation of heat. If you use Thorotrast, they don't feel a thing. You must be very careful about your injection because if you get Thorotrast outside the artery—fortunately, we have not had any such cases—you may get a granuloma, which is extremely unpleasant. The point is that Thorotrast produces complications, if any, later on, years later, and most of these patients will probably be dead before the Thorotrast can produce its complications.

The next question I have reads, "Do you think your percentage of positive angiographic findings in strokes would have been significantly increased if you had performed bilateral retrograde vertebral arteriograms in all patients?"

My immediate answer to that is no. And if one refers to our analysis of the 80 cases, basilar occlusion was diagnosed clinically in 4 instances. I imagine basilar occlusion is what the questioner is thinking of, or possibly he may be thinking of stenosis or occlusion of one or the other of the vertebral arteries at its origin which, as Hutchinson and Yates showed, is such a relatively common lesion. We confirmed it radiologically in 2 by carotid angiography, showing the reflux down the basilar artery. In 1 case we showed no abnormality; in the fourth case, we did a vertebral angiogram, or rather we tried to do a vertebral angiogram—remember, we only did 2 vertebrals in those 80 cases—and that angiogram failed.

Another point in connection with the value of vertebral angiography is that we have found it very disappointing in diagnosis of posterior fossa hematomas when hemorrhage into the cerebellar hemisphere or vermis or pons was suspected. We find that pneumography or positive contrast ventriculography is much more satisfactory. You remember that I showed one case of pontine hemorrhage demonstrated by ventriculography.

DR. SCHEINBERG: Are there any comments from the other members of the panel before I ask the other discussants to comment?

DR. WELLS: Dr. Bull, I have a question. How often is an artery not filled at the time of angiography later shown to be patent at autopsy or at operation?

DR. BULL: I find it a little difficult to answer that question competently because we do not have a large enough series of autopsy confirmations. What I would like to see is an autopsy angiogram performed on all these patients who come to postmortem examination. If we do an angiogram in life and we are not satisfied about adequate filling of a vessel which we think should be filled, we always take anteroposterior and lateral views; it may be that on one of the projections we see the vessel filled and on the other not satisfactorily filled. We would then go on to take either an oblique projection or perhaps another lateral. I don't think that one ever gets false occlusions of the main vessels, for instance, a middle cerebral occlusion. If you see on 3 projections —lateral, anteroposterior, and oblique—an occlusion of the middle cerebral artery somewhere between its origin and its bifurcation or trifurcation, I think that must be accepted as genuine.

DR. SUGAR: Several questions have been asked about the drug I mentioned in my discussion. It is commercially available from Smith, Kline and French, and the trade name is Prinadol. The generic name is phenazocine.

One of the questions that was asked is "how often is cerebral angiography of value to the patient, that is, how often can you gain information which you do not have, or, I presume, which you cannot get by some other clinical means?"

I don't know the answer to that. Certainly, if you are surgically minded, you must have angiograms for young and middle-aged persons who have blood in the spinal fluid. Whether you choose to treat older persons who bleed is another matter, but I don't think you can

operate sensibly on a bleeding lesion in the head without an angiogram. Now, as far as tumors are concerned, the diagnosis of tumors by angiography is complex. The best figures I can give you run between 70 and 80% accuracy as compared with about 95% with an air study. However, the angiogram has the advantage of telling you, if you see the tumor, where it is and, frequently, what kind of a tumor it is.

There is another question: "What percentage of patients with cerebrovascular episodes, diagnosed clinically without neurologic findings, have a diagnostic angiogram?"

Again, I can't answer that. It depends on whether it involves the left or right side and whether the patient is young or old. I probably won't do anything if a patient has had some sort of cerebrovascular episode, say temporary hemiplegia, and there are no neurologic findings at all by the time the patient is sent to me, or if the patient is young and manual carotid occlusion does not reproduce the symptoms, or if the patient is obviously reluctant to have anything done. But, on the other hand, I am very likely to go ahead and do an arteriogram if the patient and the family and the doctors are all worrying me because they are afraid this may occur again, and if it is on the right side, and if the patient has no clinical symptoms unless I produce them by carotid compression.

DR. TAVERAS: The first question is, "Do you have any evidence about the relation of stasis in intracerebral arteries to worsening of clinical states in strokes?"

There are two possibilities. As I mentioned, one is a local stasis or local slowing of circulation in the visible channels, and the other is generalized slowing in these channels. Local slowing appears to have less significance than generalized slowing and stasis within the arterial channels. I have seen generalized stasis four times in patients with acute or fairly acute syndromes, always in young patients, and they have all died. As a result, I think that, if one sees this change, one can be fairly sure that the prognosis is going to be bad. I have no evidence to indicate that, after a patient had an angiogram showing thrombosis and became worse, a repeated angiogram showed stasis.

Another question is, "When angiography demonstrates one of the anastomatic meningeal channels, that is, a functioning surface anastomosis, would you take this as evidence of interference with flow or occlusion somewhere in the normally functioning arterial channels?"

I believe that I demonstrated that this is the one way in which we can make a diagnosis of distal thromboses; that is, if we see reversal of flow, we can be fairly certain that there is occlusion.

"Is there any evidence from long-term follow-up studies that an uncomplicated successful carotid angiogram increases the risk of later carotid occlusion?"

To my knowledge, there is no such evidence in the literature. Cases such as these have not come to my attention. The pathology of acute changes in the arteries after angiography has been studied very carefully by a German group, and there are startling changes which sometimes make you wonder whether you should incur that much trauma to the arterial wall. The long-term follow-up, on the contrary, I think fails to show any correlation with increased incidence of occlusions in the future. Do you have anything to say about that, Dr. Bull?

DR. BULL: My colleague, Dr. Crawford, has examined these patients a few days after angiography and has found mural thromboses in the common and internal carotids. I agree with Dr. Taveras that we have not had patients showing up later with complications as a result of the angiogram.

Ophthalmodynamometry

James F. Toole, M.D.

ALTHOUGH OBSERVATIONS of pressure and pulsation within the retinal arteries had been made as early as 1854 by von Graefe,[1] the impetus for clinical investigation of this phenomenon came in 1917, when Bailliart[2] introduced his ophthalmodynamometer. Since then, a great body of literature has accumulated in which is recorded much fact and some fancy about the accuracy and usefulness of this technic for the measurement of retinal artery pressures. The conclusions of many of the investigators[3,4] who explored the potentialities of the ophthalmodynamometer from the 1920's through the 1940's can be summarized by saying that most were intrigued with the test but usually concluded, somewhat reluctantly, that this method for the measurement of retinal artery blood pressure did not seem to be accurate enough to be used as an investigative or diagnostic tool. They discovered many variables which prevented comparison of results from person to person. Many other factors, such as scleral and arterial rigidity, changes in systemic blood pressure, variations in intraocular tension, and change in body position, made comparison of results very difficult, even in the same individual. Because of this lack of reproducibility, the technic seemed to be dying out, or at least lying dormant, awaiting clinical application. Then came recognition of the frequency with which disease of the internal carotid artery occurs and a reawakening of interest in ophthalmodynamometry. Thomas and Petrohelos,[5] Svien and Hollenhorst,[6] Heyman, Karp, and Bloor,[7] and Wood and Toole,[8] among others, pointed out that measurement of retinal artery pressure could be a valuable aid for the diagnosis of decreased pressure within a carotid artery system. It should be said, however, that this potential had been recognized earlier by workers on the Continent, including Baurmann[9] in 1936 and Milletti[10] in 1946.

Since the arterial pressures in each eye should be equal, the most reliable application of the measurement of ophthalmic or retinal artery pressure is in those situations wherein the pressures in the two eyes may differ. One eye then serves as a control, and the multiple variables which tend to prevent comparison of results among individuals are negated. Significant pressure difference between the eyes is an indication of obstruction on the side of the lowered pressure somewhere between the aortic arch and the retinal artery. However, such a decrease in pressure must never be equated with a diminution in flow, since the latter may be maintained normally even when pressure has been markedly reduced.

A range of normal variation in pressures of the eyes has been firmly established by the above authors and by others (Fig. 1). Most have concluded that pressures in the eyes frequently equal one another but that the average difference between them is about 5% systolic and 4% diastolic, the maximum variation being 15% systolic and 10% diastolic. All believed that one need not measure intraocular tension routinely, but, whenever glaucoma is suspected or when an otherwise unexplained difference in retinal artery pressures is found, tensions must be recorded. Furthermore, because the clinician's interest is in measuring *differences* in pressure, most agree that there is little practical necessity for conversion of the grams of pressure applied to the millimeters of mercury in which one customarily expresses blood pressure. The method finds its most reliable application in processes which affect primarily one internal carotid, since pressures may be reduced equally with bilateral disease.

Although there have been no physiologic determinations to establish precisely that ophthalmic and retinal artery pressures accurately reflect the pressure within the ipsilateral carotid system, Bakay and Sweet[11] have demon-

RANGE OF NORMAL VARIATIONS IN RETINAL ARTERY PRESSURES OF THE TWO EYES

AUTHOR	NUMBER OF CASES	SYSTOLIC		DIASTOLIC	
		RANGE	AVERAGE	RANGE	AVERAGE
THOMAS & PETRONELOS	50 210 from literature	0-12.2%	6.4%	0-15%	2.7%
HEYMAN, KARP & BLOOR	44	0-10%	4.9%	0-18%	6%
SPALTER	50	0-15%	9.0%	0-10%	4%
TOOLE & REVILACQUA	17	0-13%	5.4%	0-20%	6.5%

Fig. 1. See text for explanation.

EFFECTS OF CAROTID ARTERY RECONSTRUCTION ON RETINAL ARTERY PRESSURE

	PRE OPERATIVE	POST OPERATIVE															
		1 WK.		2 WKS.		1 MO.		6 MOS.		1 YR.		2 YRS.		3-4 YRS.	
J.G.	160/80	200/0	150/90	140/90								140/70	140/80	130/90	120/90		
E.K.	130/90	80/20	150/70	150/70						140/50	130/35			135/35	100/90	120/50	110/30
I.S.	130/40	135/5	120/70	120/65	130/80	120/70	130/48	120/48	140/60	130/60						110/50	130/30
M.D.	160/30	100/40	100/40	110/40			110/35	110/30	130/35	130/30				ALL MEASUREMENTS ARE RECORDED IN GRAMS.			

Fig. 2. Note inequality of pressures preoperatively and the acute restoration toward equality after endarterectomy. Pressures have tended to be maintained equally thereafter.

strated that there is surprisingly little decrease in pressure within the internal carotid artery from its origin in the neck to its branches larger than 0.5 mm. which arborize over the cerebral hemispheres. Since the average diameter of the ophthalmic artery is 1.5 mm.,[12] one might deduce that ophthalmic artery pressures should be almost the same as those of the intracranial portions of the carotid artery and its larger branches. This seems particularly likely when one remembers that the ophthalmic artery is the first branch of the internal carotid and that just distal to its origin is a constriction which tends to maintain higher pressure within the proximal carotid and ophthalmic arteries.

Any acute lowering of carotid pressures proximal to the origin of the ophthalmic artery, whatever the ultimate cause, should be accompanied by a concomitant decrease in ophthalmic and retinal artery pressures as well as in pressures in the more distal branches of the carotid which supply the ipsilateral hemisphere. The foremost clinical use for measurement of retinal artery pressures has been in the bedside screening of patients with cerebrovascular disease suspected of having internal carotid artery obstruction. Applied thus, it is a useful and innocuous tool that gives objective data about the location of vascular abnormalities which clinical acumen and physical examination cannot always provide. When significant differences in retinal artery pressures are found in a patient whose clinical syndrome would make one suspect disease of the carotid circulation, obstruction proximal to the origin of the ophthalmic artery can be suspected. Although I have had false-positive results in which retinal pressures were reduced on one side when arteriography showed no obstructive disease, this should be no great deterrent to the use of the test for screening purposes. On the other hand, I have had 2 cases in which retinal pressures were maintained normally in the presence of an acute carotid thrombosis. This is a more serious situation, since rejection of a patient for further study and therapy on the basis of a negative

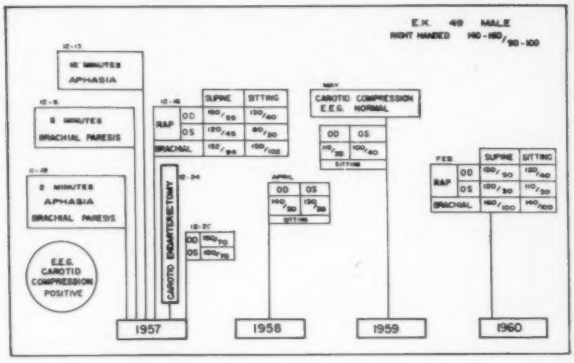

Fig. 3. Detailed consideration of one patient. Preoperatively, inequality of retinal pressures was most evident when the patient was sitting.

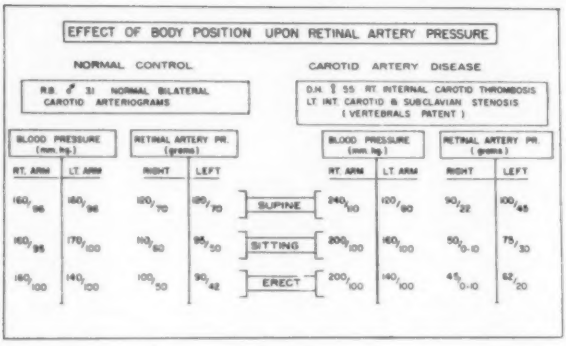

Fig. 4. Change of body position sometimes increases the inequality of retinal artery pressures.

test might be injurious. Some reasons for a false-negative test result are [1] anomalous origin or branching of the ophthalmic artery, which allows a large external carotid artery pressure to be transmitted into the ophthalmic and retinal arteries; [2] transmission of pressure through the circle of Willis into the opposite carotid system; and [3] long-standing obstruction of the internal carotid, so that external carotid collaterals have opened to restore ophthalmic pressures to normal.

This last factor is well demonstrated when one records retinal artery pressure after occlusion of the internal carotid or common carotid in the neck. In 1956, Rand[13] presented data which, among other things, plotted the course of retinal artery pressures with the passage of time after ligation of the carotid artery in the neck. It is striking to observe how ophthalmic pressure that is markedly reduced after acute occlusion sometimes rises as collaterals in the orbit and elsewhere open to restore carotid and ophthalmic pressures.

We have mentioned the usefulness of recording decreased pressures for diagnosis of carotid obstruction and for following the course of ligation of the carotid in the neck. Another important application is the objective recording of pressures after surgical reconstruction of the carotid arteries. Because we have been loath to perform postoperative arteriograms upon such patients, we have used measurements of retinal artery pressures as an index of surgical success in restoration of carotid pressure (Figs. 2 and 3).

A last clinical occurrence should be mentioned. Svien and Hooker[14] have reported that large arteriovenous malformations may be accompanied by a decrease in ipsilateral ophthalmic pressure because peripheral resistance in the carotid is diminished by the malformation. I have seen one example of this.

Time does not permit discussion of the many variables which influence the recording of retinal artery pressures. Of particular interest is the effect that body position has upon oph-

thalmic artery pressures and, presumably, upon the pressures within other carotid branches. Scheinberg and Stead[15] have shown that, in addition to reflex changes which effect cerebral blood flow, the erect posture adds hydrostatic effects which are not present when flow and pressure are measured supine. Therefore, retinal pressures in the erect position are lower than those recorded in the recumbent position. Examination in the erect position has been suggested by Smith, Zieper, and Cogan[16] as a method for bringing out latent differences in retinal pressures (Fig. 4).

In summary, I have been impressed with the usefulness of the measurement of retinal artery pressures for the diagnosis of cerebrovascular disease in which the head of carotid pressure may be reduced on one side. The test is far from absolute, and results obtained must be considered in the light of clinical history and ancillary findings.

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Carotid artery murmurs

Clinical and pathophysiologic correlation

Lamar Crevasse, M.D.

THE MURMURS associated with partial or complete thrombosis of the great vessels supplying the head and neck, particularly the carotid arterial system, are of considerable clinical value if properly interpreted. The intracranial systolic bruit, described by Cohen and Miller,[1] represents narrowing of the intracranial portion of the internal carotid at the siphon and is transmitted and heard best over the ipsilateral eyeball (Fig. 1A). This murmur also may be associated with contralateral complete thrombosis of the internal carotid artery and then reflects partial narrowing or a compensatory increase in velocity of flow across this site (Fig. 1B). Systolic murmurs over the carotid in the neck have been correlated by Fisher[2] with carotid occlusive disease. A systolic murmur may be detected over a partially occluded internal carotid artery at the angle of the jaw and may be transmitted up the carotid into the cranium and heard also over the ipsilateral eye (Fig. 1A). These bruits may be present with or without contralateral carotid thrombosis (Fig. 1B) and depend upon the degree of local arterial narrowing and upon compensatory increases in segmental velocity of blood flow. A systolic murmur likewise may be paradoxically present on the side of carotid thrombosis when turbulence of blood flow through a partially narrowed external carotid is produced by an increase in collateral flow around the occluded internal carotid artery (Fig. 1C).

A continuous arterial murmur extending through both systole and diastole may be localized over these sites and reflects severe narrowing of the vessel or compromise of its collateral arterial circulation.[3,4,5] Figure 2 shows a continuous murmur with carotid artery insufficiency which is well localized over the carotid bulb and is continuous throughout systole and diastole. No murmur is detected 5 cm. below the carotid bulb on the same side. The patient had severe narrowing of the carotid artery, with inadequacy of collateral arterial circulation to the head.

Figure 3 is a direct recording at surgery of simultaneous intravascular phonocardiograms and pressure tracings of a partially occluded left carotid artery, measured proximal and distal to the site of obstruction at the carotid bulb by the technic of Luisada.[6] A harsh, grade III systolic murmur is well localized to this site. The simultaneous pressure tracings reveal a small systolic pressure gradient across the area. This represents turbulence of blood flow only in systole, with the collateral circulation appearing adequate. Figure 4 demonstrates the temporal relationships of intravas-

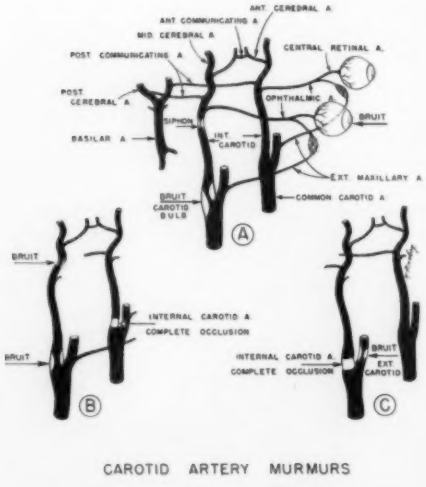

Fig. 1. Sites of carotid artery murmurs

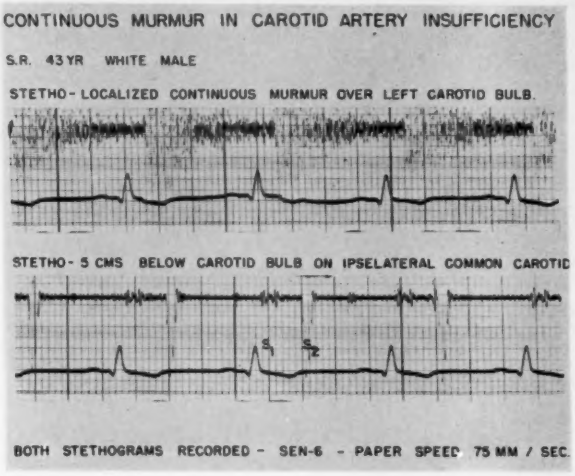
CONTINUOUS MURMUR IN CAROTID ARTERY INSUFFICIENCY
S.R. 43 YR WHITE MALE
STETHO - LOCALIZED CONTINUOUS MURMUR OVER LEFT CAROTID BULB.
STETHO - 5 CMS BELOW CAROTID BULB ON IPSELATERAL COMMON CAROTID
BOTH STETHOGRAMS RECORDED - SEN-6 - PAPER SPEED 75 MM / SEC.

Fig. 2. Continuous murmur with carotid artery insufficiency. Phonocardiogram is recorded over carotid bulb *(Top)* and 5 cm. below carotid bulb on same side *(Bottom)*.

cular sound and pressure of the right partially occluded carotid artery measured in the same patient. In the initial part of the tracing, only a systolic murmur is noted across the carotid bulb, with a small systolic pressure gradient. As this carotid artery is mechanically narrowed further, the systolic pressure gradient increases in magnitude and a diastolic pressure gradient appears. A continuous murmur is now present and reflects severe narrowing of the carotid artery and inadequacy of the collateral circulation to maintain resistance to flow in diastole. This permits blood to flow in both systole and diastole across this segment, producing a continuous arterial bruit. With complete occlusion of the carotid, the murmur disappears (Fig. 4, bottom). With gradual release of this occlusion, the continuous murmur reappears, the diastolic pressure ultimately is maintained distal to this site, and the murmur is now systolic alone. Contralateral manual occlusion of the other carotid artery would produce essentially the same tracing.

In order to study this phenomenon more carefully, the carotid and vertebral artery systems of 4 mongrel dogs were exposed and tracings were obtained. During measurement of simultaneous intravascular pressure and sounds proximal and distal to the carotid bulb, with gradual mechanical narrowing at this site, significant systolic and diastolic pressure gradients of 52 and 38 mm. Hg appeared, with no significant murmurs. The opposite carotid and vertebral artery systems were intact, maintaining peripheral resistance distal to the partial obstruction through adequate collateral cerebral circulation. Localized turbulence of blood across this site was not of significant magnitude to produce an arterial bruit in either systole or diastole. Occasionally, a systolic arterial bruit related to turbulence was recorded (Fig. 5).

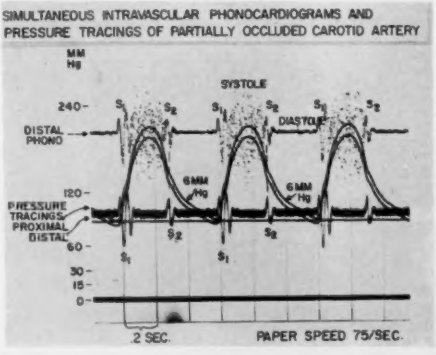

Fig. 3. Simultaneous recordings of pressure relationships and intravascular sound of partially occluded carotid, with small diastolic pressure gradient (6 mm. Hg)

When collateral circulation is reduced through ligation of the opposite internal carotid and/or vertebral systems and the remaining carotid is gradually narrowed, comparable systolic and diastolic pressure gradients appear. However, because of reduction of cerebrovascular resistance distal to the narrowed vessel, resistance to flow in systole is reduced; an increase in segmental velocity of flow produces turbulence in systole and thus a systolic murmur. With more severe narrowing, the increase of velocity of flow in diastole produces sufficient turbulence to add the diastolic component, thus causing a continuous murmur over a partially obstructed carotid, with inadequate collateral circulation to maintain adequate cerebrovascular resistance in diastole (Fig. 6).

However, murmurs over blood vessels may be associated with factors other than mechanical or anatomic narrowing. At the bifurcation of vessels and with increases in cardiac output and segmental velocity of flow, as with thyrotoxicosis or severe anemia, systolic and continuous murmurs may exist without significant anatomic narrowing. When thyrotoxicosis and anemia resolve, these murmurs may disappear completely. Furthermore, these murmurs may be only indirectly related or unrelated to coexisting neurologic symptoms. The occurrence

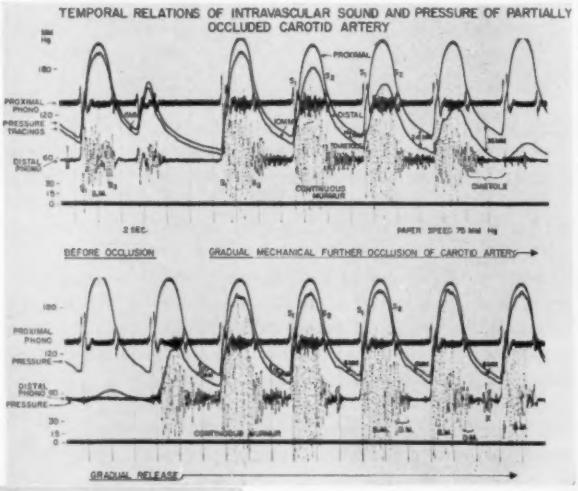

Fig. 4. Simultaneous recordings, proximal and distal of partially occluded carotid artery. *(Top)* Gradual further mechanical narrowing of vessel reveals appearance of larger diastolic pressure gradient and continuous murmur. *(Bottom)* With complete occlusion, murmur disappears. With gradual release, continuous murmur reappears, and, with reduction of diastolic pressure gradient, only systolic murmur remains.

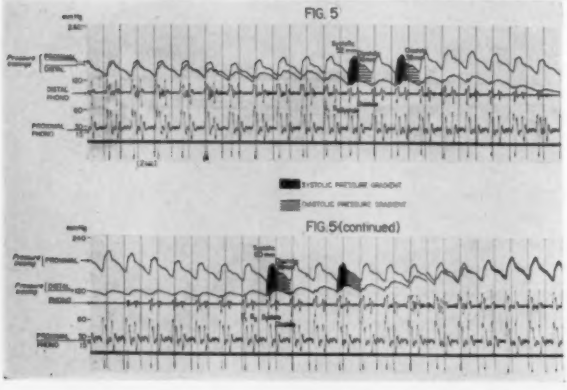

Fig. 5. Control tracing of gradual narrowing of carotid artery in dog, with opposite carotid and vertebral systems patent

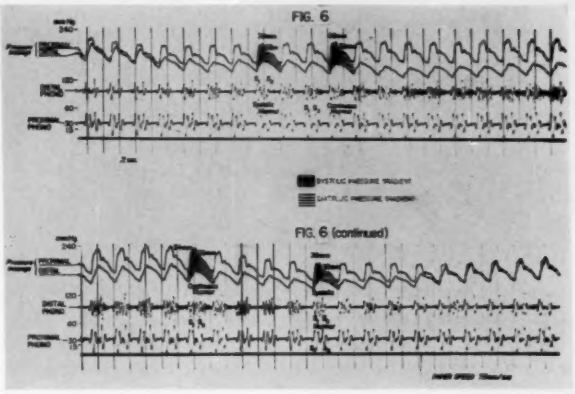

Fig. 6. *(Top)* With opposite carotid and vertebral arteries ligated, prominent systolic, and ultimately continuous, murmur appears over site of graduated mechanical carotid narrowing. Essentially, same systolic and diastolic pressure gradients are present as in Figure 5. *(Bottom)* With gradual release of obstruction, murmur and pressure gradients disappear.

of murmurs and neurologic symptoms may be fortuitous, and care should be exercised in drawing conclusions. Systolic and continuous murmurs thus may coexist with signs and symptoms primarily related to basilar artery insufficiency. However, these murmurs are a direct reflection of inadequate collateral circulation to the basilar system, and the symptoms may be due in part to partial narrowing of the carotid system.

Murmurs and subjective noises have been observed with carotid insufficiency by both physicians and patients. When the lumen narrows because of atheromatous deposits, usually at the carotid bulb, a systolic murmur appears. As the lumen further narrows and if collateral circulation is inadequate to maintain peripheral resistance distal to the site of obstruction, a continuous murmur appears. Transient symptoms, precipitated by hypotension of any cause, may occur on the side opposite the obstruction. In this group of patients, the neurologic examination most likely will be normal and the only physical finding may be a systolic or continuous murmur over the partially occluded carotid depending upon the status of the collateral circulation. Surgery may alleviate symptoms and prevent later complete thrombosis. With complete occlusion, the murmurs and subjective noises will cease and irreversible neurologic symptoms may appear.

To summarize, localized carotid arterial bruits are clinically helpful in detecting the site of partial carotid arterial narrowing and in assessing the status of the collateral arterial circulation.

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Discussion of ophthalmodynamometry as a diagnostic procedure

Albert Heyman, M.D.

THE DETERMINATION of retinal artery pressure by ophthalmodynamometry and auscultation of the head and neck for bruits have become two of the more useful adjuncts to the bedside diagnosis of carotid artery occlusion. Although neither procedure is completely reliable, both are, in our experience, more helpful than such other commonly used tests as compression of the contralateral carotid artery or pharyngeal palpation for diminished or absent carotid pulsation. Both latter procedures have limited diagnostic value and, indeed, in the case of carotid artery compression, may be dangerous to the patient. Needless to say, arteriography remains the most reliable diagnostic method.

Ophthalmodynamometry not only is becoming a routine procedure in the diagnosis of carotid insufficiency but also is proving to be a useful tool in evaluating the results of vascular surgery in the neck and in determining the effectiveness of surgical closure of the common carotid artery in the treatment of intracranial aneurysms.[1]

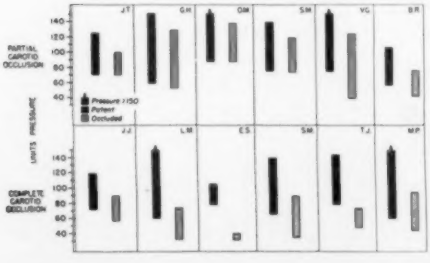

Fig. 1. Comparison of retinal artery pressures in patients with partial or complete carotid occlusion as demonstrated by arteriography

It should be remembered, however, that even patients with complete carotid occlusion do not always have a reduction of ipsilateral retinal artery pressure. Such false-negative tests are, as pointed out by Dr. Toole, probably the result of collateral circulation to the ophthalmic artery, either by way of the circle of Willis or through anastomoses from the external carotid system. In our own experience, such cases are not infrequent. On the other hand, we have seen only 1 patient with persistent reduction in retinal artery pressure in whom the ipsilateral carotid arteriogram failed to show a definite obstruction. In this patient, the vessel showed evidence of tortuosity and diffuse sclerosis, which may have impaired its blood flow sufficiently to reduce the retinal artery pressure.

The degree of reduction of ipsilateral retinal artery pressure in patients with partial carotid occlusion may be quite small. In such cases, it may be overlooked unless careful determinations, measuring both systolic and diastolic retinal artery pressures, are made. A comparison of the retinal artery pressures in partial and complete carotid occlusions is shown in Figure 1. Of the 6 patients with partial occlusion, 3 showed little or no differences in retinal diastolic pressures and only slight differences (less than 25%) in systolic pressures.[2] In contrast, patients with complete carotid occlusion often had wide differences in retinal artery pressures. Since surgical therapy of carotid thrombosis is usually more successful in cases of partial occlusion, the diagnosis of this condition becomes of practical importance. However, the effects of partial carotid occlusion on retinal artery pressure are difficult to predict because of variation in collateral circulation in the individual patient.

Not only does the degree of carotid closure affect the retinal artery pressure, but the duration of the occlusion is also thought to be an important factor. After carotid artery occlusion, gradual development of collateral circulation would be expected to restore blood flow through the ophthalmic artery and to bring about equal retinal artery pressures. We have observed the changes in retinal artery pressures in 10 patients for as long as three to nineteen months after surgical closure of the common carotid artery in the treatment of intracranial aneurysms.[3] Immediately after closure of the common carotid artery by a Crutchfield clamp, mean reduction of ipsilateral retinal artery pressure was 28%; at the end of an average period of twelve months' observation, the mean reduction was 23%. Only 1 patient (I.M.) failed to maintain a significant reduction of retinal artery pressure (Fig. 2). The remaining patients continued to show a definite decrease in retinal artery pressure ipsilateral to the occlusion during this period of follow-up observation.

As mentioned previously, ophthalmodynamometry has become a useful method of determining the effectiveness of surgical closure of the common carotid artery. The patient illustrated in Figure 3 shows a reduction of retinal artery pressure immediately after carotid occlusion with a Crutchfield clamp. Four months later, however, circulation apparently was restored, since the retinal artery pressures became equal. A loud bruit also developed in the neck over the carotid artery. Reexploration of the vessel revealed that it was not completely closed, and readjustment of the clamp once again produced an ipsilateral reduction of retinal artery pressure.

There is no doubt that the external carotid system may occasionally restore retinal artery pressures after prolonged carotid occlusion.[3] Figure 4 illustrates the retinal artery pressure changes in a patient who had an arteriovenous malformation in the distribution of the right middle cerebral artery. After ligation of the right common carotid artery, the retinal artery pressures showed characteristic differences. One year later, the retinal artery pressure had become equal in both eyes and the patient noticed the return of the intracranial bruit. At this time, ligation of the external carotid

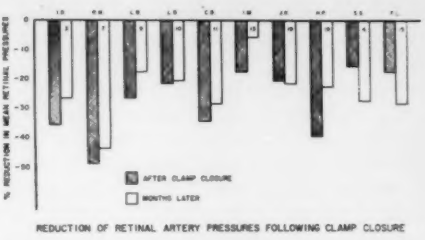
% REDUCTION IN MEAN RETINAL PRESSURES
AFTER CLAMP CLOSURE
MONTHS LATER
REDUCTION OF RETINAL ARTERY PRESSURES FOLLOWING CLAMP CLOSURE

Fig. 2. Comparison of immediate and late mean retinal artery pressures after clamp closure of common carotid artery. Figures in open bars indicate number of months after carotid closure.

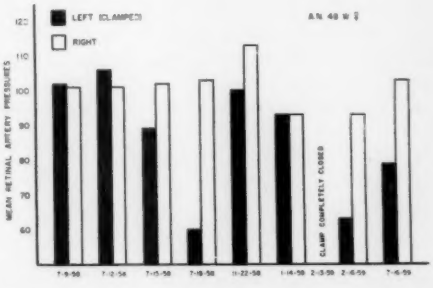

Fig. 3. Retinal artery pressures in a patient with restoration of carotid circulation after partial occlusion of vessel with Crutchfield clamp. Readjustment of clamp with complete closure again produced significant reduction in ipsilateral retinal artery pressure.

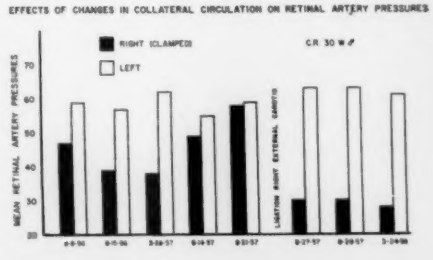
EFFECTS OF CHANGES IN COLLATERAL CIRCULATION ON RETINAL ARTERY PRESSURES
RIGHT (CLAMPED)
LEFT
MEAN RETINAL ARTERY PRESSURES
LIGATION RIGHT EXTERNAL CAROTID

Fig. 4. Changes in retinal artery pressures after restoration of carotid circulation by way of ipsilateral external carotid artery. Ligation of this vessel produced significant decrease in ipsilateral retinal artery pressure.

artery produced a significant and persistent reduction in the ipsilateral retinal artery pressure.

The role of the ipsilateral external carotid artery in restoring the pressure in the distal carotid system was also determined in 7 other patients with surgical closure of the common carotid artery.[3] In each of these cases, retinal artery pressures were measured before and during manual compression of the neck above the site of the closure. Since the common carotid artery presumably was completely occluded, a reduction of the retinal artery pressure after this maneuver indicated the amount of collateral circulation supplied to the ophthalmic vessels by the external carotid artery. During compression of the neck, the ipsilateral retinal artery pressure in these 7 patients fell 8 to 34%, with a mean of 22%. Although direct arterial pressure measurements at the time of common carotid occlusion indicate that the external carotid artery does not contribute significantly to collateral blood flow,[4] this situation seems to change soon afterward. Apparently, approximately one-fourth of the residual pressure in the internal carotid system is due to collateral circulation supplied by the ipsilateral external carotid artery. Whether thrombotic disease of the common or internal carotid artery is associated with a similar degree of collateral blood flow is not known, but such a situation seems probable.

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General discussion on ophthalmodynamometry, second session, May 1, 1960

Dr. Peritz Scheinberg, Chairman

DR. SCHEINBERG: Dr. Sugar, from a neurosurgical point of view, do you have any comments about the use of these ancillary technics?

DR. SUGAR: The principal difficulty that I have is in getting someone to do the test. We have not used it as often as we should, and I am convinced that this is probably as useful, although not as dramatic, a test as carotid compression. Consequently, in view of the complications which are reportedly very frequent with carotid compression tests, perhaps we ought to use the ophthalmodynamometer more often than we do. I am impressed with the utter divergence in opinion that one can get right here in this room as to whether the retinal pressures stay down years after carotid occlusion by a clamp or whether they stay up or whether some stay up and some stay down. This is a very important question for us because one of our big problems is trying to win people over to the concept that carotid occlusion in the neck is as valuable for many aneurysms as the more hazardous intracranial approach. If we can show or have someone else show that the pressure stays down for a long time, we have a talking point to those neurosurgeons who say you must go inside the head because that is the only way you can be sure that you have permanently stopped the bleeding point. If one of you some day will accumulate enough experience and statistics to be able to convince the rest of the neurosurgeons that carotid occlusions in the neck have a long-lived, but not too long-lived, drop in retinal pressure, I should be happy.

DR. WEISS: Dr. Toole, would you comment on the relation of cardiac arrhythmias to ophthalmodynamometry and the accuracy of binocular versus monocular measurements.

DR. TOOLE: I would like to begin by attempting to lift the mantle of ultraspecialization that has been cast upon my shoulders and to answer Dr. Sugar by saying that I don't believe that it is necessary for an ophthalmologist to do the test. Any physician who sees patients with cerebrovascular disease can learn to perform this test without any particular training other than a few weeks of attempting to do it, if he is facile with his ophthalmoscope.

One of the questions is about my technic: What does it consist of? Do I anesthetize the eye? Do I dilate the pupils and so forth?

Depending upon the cooperation of the patient, one has variable success in the performance of this test. Frequently, the patients in whom we are most interested are the ones that cannot cooperate sufficiently to allow the test to be performed, that is, the comatose or irrational ones. I like to do the test with the patient sitting. I ask him to fix on a distant object. I do not ordinarily dilate the pupils, nor do I use a corneal anesthetic. If I were testing the right eye, I would ask him to gaze somewhat to the left. I place the instrument laterally on the sclera, and then I have the patient look forward again, explaining to him what I am doing, and then rather rapidly increase the pressure on the gauge so that the diastolic levels are reached.

Another question is whether the diastolic pressure alone is sufficient.

My answer to that is that I don't think so, although some other persons routinely measure only the diastolic pressures.

I have had no complications, but, just talking with members of the audience in the last few minutes, I have heard of one instance of a patient who had a retinal artery occlusion

after the test and of another who had a few minutes of amaurosis. Other than subconjunctival hemorrhages, I have had no complications from the test.

One of the other questions was, "Do I use an assistant?"

Some persons use assistants, one looking into the eye with an ophthalmoscope and the other applying the pressure. I do it all myself. In addition to that, I ordinarily measure the pressure with the patient sitting or, if necessary, in the supine position.

I would like to change the subject now to auscultation. As part of my complete diagnostic work-up, I listen not only over the carotid arteries but also over the vertebrals. I have been impressed with how frequently I can hear murmurs at the supraclavicular space over the subclavian artery which may be transmitted up the cervical spine and even into the occipital region. These are not necessarily murmurs transmitted from the carotid system at all, because the common carotid can be compressed and the murmur will continue. When the vertebral or subclavian is compressed, the murmur will stop. On the basis of a murmur and a thrill, I have been able to diagnose lesions at the base of the neck at the subclavian-vertebral junction in a few patients with basilar artery insufficiency. This was confirmed by arteriography of all 4 vessels.

Another interesting observation, I think, is that these murmurs will sometimes vary with the position of the head on the neck. Probably, the torsion of the vessels and relationships of the vertebral artery in the cervical spine are altered by a change of the position of the head.

There is one last question: "Is it technically easy to determine retinal systolic pressure?" My answer is yes, I think that it is quite easy.

DR. SCHEINBERG: Dr. Toole, where do you put the stethoscope when you listen to the vertebral artery? That is not quite clear.

DR. TOOLE: Most cardiologists listen to the aortic area and the pulmonic area, and, if they suspect a murmur here, they will listen to the base of the neck from transmission. By listening a little bit further distally, one can auscultate over the carotid sinus at the bifurcation in the neck and on up anteriorly and, as Dr. Miller Fisher has pointed out and emphasized, over the orbits. As far as the vertebral murmurs are concerned, in the supraclavicular space just above the clavicle, one can frequently palpate the subclavian artery where it is traversing medially and posteriorly. By placing the stethoscope over that region, one can frequently hear a systolic murmur and occasionally palpate a thrill.

DR. SCHEINBERG: Dr. Crevasse, is there any particular value or danger associated with palpating the carotid artery in the tonsillar fossa?

DR. CREVASSE: I don't think that there is any particular danger in palpating the internal carotid artery in the fossa or even partially occluding it in the neck temporarily. I know that there are reports contrary to this, but we have not encountered this difficulty even though we have examined a large number of internal carotids in this fashion. The problem of palpating the internal carotid artery as it courses through the tonsillar fossa has three limitations. First, it is difficult to do and takes practice. The patient should be on his back; you should use a rubber glove and wet it beforehand. You can occasionally use procaine lozenges to anesthetize the back of the throat. Second, spasmodic contractions of the pharyngeal musculature, even though there may be a complete occlusion of the internal carotid on one side, will simulate pulsations, and you must contrast them with the pulsations of the opposite internal carotid. You may also have lateral transmission into the tonsillar fossa of pulsations from the external carotid artery which will simulate pulsations of the internal carotid. And, third, when you feel pulsations on both sides and they seem symmetric, you may still have thrombosis of the internal carotid artery on one side because the thrombosis may be higher in the artery at the siphon; this does not exclude the diagnosis.

I think that palpation will help you in the diagnosis of complete occlusion, but auscultation gives much more information. It tells you whether the patient has a partial occlusion. If the outflow tract is good, the chances are excellent that you will be able to restore blood flow and alleviate the symptoms.

There are several other questions: "How would you clinically distinguish between bruits over the carotid due to stenosis and those transmitted from an arteriovenous fistula?"

The murmur is very similar to one produced

by an arteriovenous fistula. Indeed, the first time I heard a carotid murmur I thought it was from an arteriovenous fistula in the neck. It is continuous like the murmur of a patent ductus or an arteriovenous fistula. The arteriovenous fistulas in the neck in this region are usually associated with the thyroid artery; if you occlude the carotid artery above this area, the continuous murmur related to the thyroid arteriovenous fistula or the thyroid gland itself will continue. This murmur over the carotid bulb, which is continuous, will diminish if it is related to a carotid bulb partial occlusion. If the arteriovenous fistula were overlying the carotid bulb, I do not think there would be a way to distinguish it, unless you could obstruct the venous outflow and abolish the arteriovenous fistula.

And the last question is, "How often are subjective systolic murmurs found in the absence of intracranial vascular disease?"

I think that they occur; I don't know the exact incidence. I believe that, frequently, tortuousity of vessels in the head produces systolic noises. In general, the patients with subjective noises in the head related to partial occlusion of the internal carotid artery have symptoms that are quite prominent because the murmurs are very loud. The flow is very rapid, producing a high-intensity murmur.

I too, have had the same experience with bruits in vertebral artery insufficiency that Dr. Toole points out. I think auscultation there is very valuable. We have also used auscultation with cardiovascular disease, which has frequently enabled us to determine the degree of obstruction of the femoral artery or the degree of obstruction of the vessels as they arise from the aorta.

DR. HEYMAN: First of all, I would like to emphasize the fact that, although bruits from the carotid artery are often heard directly over the narrowed vessel, occasionally a cranial bruit is heard on the side opposite the occlusion. This is on the side of the patent carotid artery, and a bruit is often heard over the orbital area. Apparently, a bruit on the side opposite the occlusion reflects increased speed or turbulence of blood flow, in order to supply both the normal hemisphere as well as a portion of the involved hemisphere. We recently observed a patient in whom a very loud bruit developed over the opposite artery after surgical ligation of one carotid artery.

The first question is, "What percentage of ophthalmodynamometry recordings do you estimate are false-positive and false-negative?"

In my experience, I have had only one false-positive test. False-negatives, I think, are more frequent, although this again is a matter of individual experience. I would estimate that they occur in 15% of patients, but this is purely an estimate. I believe that it depends, as so many other things do, upon the experience of the examiner and the care with which the recording is done. We usually have two persons performing the examination although others do not.

"Are there any complications or is the procedure completely harmless?" That has been answered. In our own experience, we have had only a subconjunctival hemorrhage. I think it is important to emphasize here, too, that this procedure is not always simple. The patient may be unconscious or uncooperative. Patients who have third nerve palsies have their eyes directed outward, and you may have difficulty getting the instrument on the sclera and avoiding the cornea.

"In what percentage of patients with carotid insufficiency do you find reduced retinal pressures?"

My own guess would be about 75%.

"How rapidly does collateral circulation affect ophthalmodynamometric readings after occlusion of the internal carotid artery?"

As I mentioned, Dr. Woodhall and Dr. Odom have recorded intravascular pressures before, during, and immediately after carotid occlusion and ten to fourteen days after that. Most of the patients will show an increase in the residual carotid pressure distal to the occlusion, but this is usually very slight. The retinal artery pressure almost always remains reduced for weeks and months. As I mentioned, many of our patients have gone as long as nineteen months to two years with reduced ipsilateral retinal artery pressures. I think that our findings indicate that not more than 20% of the patients have a restoration of collateral circulation as measured by this technic. Perhaps this would help to support the use of carotid artery occlusion in the management of intracranial aneurysms.

The electroencephalogram in cerebrovascular diseases

H. Gastaut, M.D., and F. Poirier, M.D.

BRAIN DAMAGE resulting from acute vascular lesions (arterial and venous occlusion or rupture, hemorrhage, or infarction) gives rise to the following electroencephalographic signs: [1] an immediate electrical silence over the destroyed area, and, later, [2] slow waves around that area.

Visual and automatic frequency analyses of the electroencephalographic records help greatly in establishing the site and nature of the damage, which can be inferred from the localization and evolution of the slow waves and the eventual changes in the basic rhythms, either spontaneous or evoked.

On the other hand, chronic cerebrovascular insufficiency, resulting from arteriosclerotic narrowing of intra- and extracranial arteries, constitutes a purely functional problem; indeed, pathologic changes occur only with a superimposed lowering of blood pressure. Then, the insufficiency is not chronic any more but acute. If this acute phase is sufficiently prolonged, parenchymatous necrosis and softening ensue; if transient, it causes only a temporary depression of cerebral function. This depression, nevertheless, results in "ischemic seizures," often followed by postictal paralysis and too frequently confused with epileptic seizures. Clinically latent features of chronic cerebrovascular insufficiency have prompted its more adequate detection by complementary diagnostic methods, notably electro- and rheoencephalography. This paper deals only with the latter aspect of the problem.

ELECTROENCEPHALOGRAPHY

1] The resting records of patients with cerebrovascular insufficiency show more or less regular sinusoidal slow waves, occurring in fusiform bursts of 4 to 5 elements, superimposed on a more or less normal basic rhythm, and appearing in the Sylvian region of the less vascularized hemisphere, usually the left (occasionally on both sides).

2] Nitrogen inhalation causes an increase in slow waves and leads even to their replacement by hypersynchronous delta dysrhythmia, which diffuses over the involved hemisphere before spreading to the other.

3] Inhalation of a mixture of CO_2 and O_2, on the contrary, abolishes these "ischemic Sylvian slow waves" and helps distinguish them from nonfunctional slow waves due to other causes such as softening and tumor.

4] Carotid compression on the involved side brings out more slow waves and leads to their overshadowing by bursts of hypersynchronous delta waves over the ipsilateral hemisphere. In cases of carotid thrombosis, compression of the patent carotid artery results in slow waves on the side of the compression. In cases of basilar occlusion (the collateral circulation to the posterior cerebral artery coming from the carotid system), carotid compression results in the appearance of slow waves in the posterior part of the hemisphere ipsilateral to the compression.

5] Compression of the carotid sinus of arteriosclerotic patients causes reflex cardiac inhibition and chiefly vasodilation. A significant drop in blood pressure leads to generalized cerebral ischemia and syncope, associated with bilateral slow waves. A slight lowering in blood pressure, on the other hand, leads to ischemia and slow waves on the side of the compression only.

RHEOENCEPHALOGRAPHY

Rheoencephalography is a method of plethysmographic recording; it has now been

sufficiently perfected as to yield valuable information on cerebral circulation and its variations in any part of a hemisphere. By comparing tracings obtained from symmetric areas of the brain, one can [1] detect and localize chronic cerebrovascular insufficiency and [2] assess the adequacy of the anastomosing circuits necessary for revascularization of one carotid territory from the other carotid or the vertebral arteries.

In conclusion, electroencephalography and rheoencephalography can confirm a diagnosis of chronic carotid or middle cerebral artery insufficiency in a great number of cases, of basilar artery insufficiency in fewer instances, and, in addition, of carotid sinus hypersensitivity, itself responsible for lowering of blood pressure and sometimes acute cerebrovascular accidents. These methods help to distinguish ischemic from epileptic seizures and finally allow functional evaluation of intracranial anastomoses before surgery.

Since chronic cerebrovascular insufficiency and carotid sinus hypersensitivity both depend on intra- and extracranial atherosclerosis, polygraphic recordings are bound to have a decisive role in the study of cerebral complications of atherosclerosis.

SUMMARY

1. The electroencephalographic signs of acute cerebrovascular accidents are mentioned.

2. The "functional" nature of chronic cerebrovascular insufficiency is stressed. Because of the paucity of clinical signs of this condition, great reliance is given to its detection by polygraphic methods, notably electroencephalography and rheoencephalography.

3. Signs of chronic cerebrovascular insufficiency are reviewed as they occur in resting electroencephalographic records, after inhalation of nitrogen and of a CO_2-O_2 mixture, and with compression of the carotids and of the carotid sinus. The value of rheoencephalography in allowing a functional evaluation of cerebral collateral circulation is pointed out.

4. The advantages of these methods in confirming a diagnosis of carotid and basilar insufficiency and of carotid sinus hypersensitivity, in establishing the nature and site of a lesion, and in distinguishing ischemic from epileptic seizures are discussed.

This paper contains in abstract form the authors' more extensive contribution to the 1959 Colloquium of Marseilles, now published in:

MEYER, J., and GASTAUT, H.: Cerebral Anoxia and the Electroencephalogram. Springfield, Ill., Charles C Thomas 1960.

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Discussion of "The Electroencephalogram in Cerebrovascular Diseases"

Charles E. Wells, M.D.

We are greatly indebted to Professor Gastaut and the school of Marseille for their endeavors over the past several years which have so expanded our knowledge of the electrophysiology of cerebral anoxia. I should like to examine Professor Gastaut's paper today in respect to what he has left unsaid, as well as to what he has said, and to pose the question: "Can we now, by combining earlier observations with those just presented, evaluate the clinical role of electroencephalography in cerebrovascular diseases as a whole?"

Professor Gastaut has not dealt in any detail with the electroencephalographic changes in structural alterations such as cerebral hemorrhage or infarction. It is pertinent to ask whether such an omission is justifiable—justifiable, that is, not because of the limited time available for these presentations but justifiable by its lack of clinical significance. For electroencephalography to be of value clinically in structural or functional cerebrovascular disease, it must fulfill 3 criteria: [1] the electroencephalogram must show alteration when functional or structural abnormality is demonstrated clinically; [2] the electroencephalogram must differentiate dysfunction secondary to vascular disease from dysfunction due to other causes such as tumor or epilepsy; [3] the electroencephalographic abnormality should not occur with any significant frequency in a patient free of clinical signs and symptoms of disease.

Since the first systematic studies of the electroencephalogram in cerebrovascular disease published in 1948 by Strauss and Greenstein[1] and Cohn and associates,[2] it has been known that cerebrovascular lesions, whether hemorrhagic, embolic, or thrombotic, may be associated with changes in the electroencephalogram. Since then, numerous studies have demonstrated electroencephalographic alteration with lesions of the brain due to disease of the vessels supplying the cerebral hemispheres and the brain stem. The findings are in general agreement: a vascular lesion of the brain is often associated with depression of alpha activity over the involved hemisphere, and, in addition, a focus of abnormal theta or delta activity is frequently present. Unfortunately, such records often cannot be differentiated from those taken in patients with cerebral neoplasm. Furthermore, the electroencephalogram may show no abnormality at all. Studies in recent years have shown that normal records are frequently seen in patients with brain stem vascular disease.[3–5] This has at least helped to explain some of the instances where severe clinical dysfunction due to vascular disease has occurred in the presence of a normal electroencephalogram.

Since a single waking electroencephalogram with vascular disease was so frequently unrewarding, attempts were made to refine the testing methods. Sleep,[6–9] barbiturate activation,[8,9] and intermittent photic stimulation[10,11] were all employed. While, as expected, these activation technics sometimes demonstrated electroencephalographic abnormalities where none had been noted before, they obviously failed to define the nature of the underlying pathologic process. Perhaps the most valuable means of differentiating the electroencephalogram with cerebrovascular accident from that with tumor is the different evolution of the electroencephalogram in the two diseases. After a cerebrovascular accident, serial electroencephalograms usually show improvement, whereas, with tumor, they usually show deterioration. Thus, Roseman, Schmidt, and

Foltz[12] in their extensive study of 1,000 patients found the improvement in serial records as perhaps the most characteristic feature of the electroencephalogram with vascular diseases. They alluded though to the fact that records do not necessarily improve with vascular accidents. More recently, there have been a number of well-documented instances in which the electroencephalogram with vascular disease showed deterioration[13,14] and, conversely, instances in which the electroencephalogram with tumor showed improvement.[13–15]

Thus, I must conclude that Professor Gastaut is well justified in treating the electroencephalogram with structural cerebrovascular changes so briefly. It is true that the electroencephalogram may aid in precise localization of the lesion, that a normal pattern may point to brain stem rather than hemispheric disease, and that a resolving pattern favors vascular accident over tumor. But, as a guide to the physician in the care of patients suspected of having cerebral hemorrhage, thrombosis, or embolism, the over-all benefits obtained from the electroencephalogram are disappointing.

Let us turn to the electroencephalogram with functional vascular disease of the brain as detailed by Professor Gastaut. Several years ago, Denis Hill,[16] in commenting on the paucity of information obtained from the single electroencephalogram taken during the waking state, opined "that the use of the electroencephalograph as a single standardized test will be superseded in time by a series of detailed special investigations, planned in advance to answer certain quite specific questions about the cerebral functioning of the patient." Professor Gastaut has taken this concept of examination of functional capacity to its greatest extent thus far.

Ignoring for the moment the importance of these observations in providing a conceptual framework of cerebrovascular dysfunction, let us examine these studies in the light of their possible clinical utility. In other words, admitting the functional singificance of these concepts, how much can these methods of study aid us in management of the patient suspected of having cerebrovascular disease?

As Professor Gastaut himself has previously emphasized,[17] these runs of slow activity in the temporal regions which he ascribes to chronic cerebral circulatory insufficiency are not synonymous with clinical cerebral circulatory insufficiency. Silverman, Busse, and Barnes[18] described such electroencephalographic findings in 25% of their subjects over 60 years of age, all of whom were found free of any evidence of cerebral malfunction. Perhaps these electroencephalographic changes may be likened to the electrocardiographic changes associated with left ventricular hypertrophy, where electrographic evidence of change in function also does not necessarily imply clinically symptomatic disease. Since inhalation of nitrogen is said to increase the prominence of these slow waves, I should like to know whether this also occurs in normal asymptomatic elderly subjects who have slow waves in the temporal region. Conceivably, those subjects showing signs and symptoms of disease might respond differently from those who are asymptomatic.

Several years ago, Waltz, von Weiss, and Stevens[19] studied the effect of breathing 7% carbon dioxide upon the focal slow wave activity in patients with cerebral infarction. Using the Hoagland delta index, they found that carbon dioxide inhalation was accompanied by a statistically significant decrease in cerebral slow wave activity in 50% of the patients studied. We have recently been trying to confirm these observations in patients with cerebral infarction.[20] Preliminary survey of our results in about 40 patients has been disappointing. However, I should emphasize that our detailed evaluation is not yet complete, and our final opinion on this procedure must be reserved for the future. Our experience with carbon dioxide inhalation in patients with chronic cerebral circulatory insufficiency of the types described by Professor Gastaut is too meager as yet to be meaningful. Again it would be valuable to know the response to carbon dioxide in those asymptomatic subjects demonstrating this temporal slow wave abnormality.

The diagnostic value of carotid compression with thrombosis of the internal carotid and anterior cerebral arteries is well known; its value with chronic cerebral circulatory insufficiency has been further emphasized here. With a procedure of such proved diagnostic

usefulness, it is important to emphasize that a positive response to carotid compression does not automatically eliminate the presence of disorders other than vascular insufficiency. Professor Gastaut[17] has described its rare occurrence in patients with traumatic, neoplastic, infectious, or degenerative cerebral disorders. Dr. Weiss[21] has described a positive response to carotid compression in a patient whose vascular supply was embarrassed by the surrounding growth of a meningioma. Webster and Gurdjian[22] found 6 positive responses in 26 subjects with brain tumors or hematomas. Terzian[23] has seen positive responses in patients with intracerebral tumors and subdural hematomas, and Garde, Fournet, and Lanternier[24] have also observed this phenomenon in 4 patients with cerebral neoplasm. While false-positive responses are rare, they do occur. Thus, the physician must recognize that a positive response to carotid compression does not guarantee that the etiology of the underlying disease is vascular.

As for rheoencephalography as a diagnostic technic, I have no personal experience. We must congratulate Professor Gastaut on the ingenuity of this new method of study.

In summary, there are definite, though perhaps minor, limitations to the use of these diagnostic measures in clinical management. These limitations should in no way dim the significance of the functional concepts for which these studies have provided a basis. We are greatly indebted to Professor Gastaut, for by his observations and his synthesis we are able to link theoretically the electroencephalographic abnormality present in many asymptomatic elderly subjects to those present with chronic cerebral circulatory insufficiency and, further, to those present in later stages of disease when structural alterations have supervened. Thus, Professor Gastaut has given us a more tenable concept of cerebral circulatory pathophysiology than has previously been afforded.

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Discussion of "The Electroencephalogram in Cerebrovascular Diseases"

Stuart Weiss, M.D.

I FEEL HIGHLY HONORED to have the privilege of discussing Dr. Gastaut's paper. As he states, our concept of the production of chronic and, more important, acute cerebrovascular insufficiency syndromes is a functional one. Transient neurologic deficit, with periods of normality between, occurs when the collateral circulation to a compromised area of brain cannot be maintained. Infrequently, sudden drops in systemic blood pressure or decreases in cardiac output precipitate such a situation. More often, the cause is local and arteriosclerotic.

Widening recognition of the significance of the insufficiency syndromes has shifted the emphasis in cerebrovascular disease to prophylactic measures and treatment of the underlying condition. Successes with anticoagulation and vascular surgery have necessitated development of functional diagnostic tests to evaluate patients suspected of having this condition.

In 1956, Meyer and Denny-Brown proposed postural tilt, utilizing the orthostatic drop in systemic blood pressure with and without the added stress of carotid compression to precipitate electroencephalographic change. A positive result indicated failure of primary or collateral circulation or both. We also were intrigued with the possibilities of using this procedure as a provocative test of incipient failure of collateral circulation.

With tilt alone, our vascular insufficiency subjects did not have associated electroencephalographic change. Such a tilt occasioned insignificant pulse rate change and a minor blood pressure drop similar to those found in a group of age- and sex-matched controls. This maintenance of systemic pressure would explain the absence of electroencephalographic change if this were the only determining factor.

Since tilt alone did not produce positive results, a careful evaluation of the effect of carotid compression with tilt assumes added importance. Carotid compression during tilt produced electroencephalographic change in both our vascular insufficiency subjects and our matched control group. The electroencephalographic changes were associated with moderate bradycardia during carotid compression in several in the insufficiency group and in a majority of the control group. Those of both groups who had no electroencephalographic change had a relatively stable carotid sinus mechanism. Thus, a sensitive carotid sinus, when stimulated during compression, may produce a cardioinhibitory or vasodepressor effect contributing to a total decrease of blood flow to the brain. This might explain the electroencephalographic changes that occur in patients with a thrombosed carotid or in those with basilar insufficiency. These complications of carotid sinus sensitivity (especially the vasodepressor response) are reduced by carrying out carotid compression with the patient in a horizontal position. Other modifications in technic, such as compressing the carotid artery above the sinus at the angle of the jaw, local infiltration in the region of the carotid sinus with procaine, and premedication with large doses of intravenous atropine are known to reduce the amount of cardioinhibitory response. Then the major determinant of electroencephalographic change upon carotid compression becomes the degree of collateral circulation to the compromised area of brain. A small percentage of patients with clinical insufficiency syndromes will not manifest electroencephalographic change under these conditions; however, examination in the supine position does provide a more critical provoca-

tive test in that the number of false-positive electroencephalograms in the control group is markedly reduced. Thus, the individual patient can be more accurately evaluated with regard to the functional status of his cerebral circulation, and negative results are of diagnostic and prognostic value.

Notwithstanding recent advances in arteriographic methods and surgical technics, the most frequent mode of treatment of acute and recurrent insufficiency states, especially basilar-vertebral artery disease, is by means of anticoagulation. Rationale for anticoagulation therapy is primarily based upon clinical response with relatively little objective evidence for the efficacy of this therapy. Disappearance of transient electroencephalographic abnormalities associated with tilt and carotid compression has been noted after anticoagulation, this being correlated with an improved clinical state.

Recently, we surveyed 13 patients with carotid artery insufficiency and 8 patients with basilar artery insufficiency who have been maintained on anticoagulation therapy for periods of six months to three years without recurrence of neurologic deficit. None had electroencephalographic changes with rapid tilt alone, and blood pressure and pulse rates remained stable during the procedure. In each group, 4 withstood carotid compression in horizontal and vertical positions, showing no electroencephalographic change. Of the 9 positive subjects with carotid insufficiency having compression in the supine position, 7 had focal or generalized slow activity with accentuation on the side of compression.

Several noted paresthesias or sensory loss in the contralateral hand, and 1 subject transiently lost consciousness. In another, symptoms and electroencephalographic changes were precipitated by rotation of the head, suggesting mechanical occlusion of the carotid circulation as the mechanism. Of the 4 patients with basilar insufficiency, 3 had asymmetric parietooccipital delta activity or generalized slowing, with posterior accentuation upon compression of 1 carotid in the supine position. None had associated clinical phenomena. There appeared to be little difference in the frequency of positive results in the anticoagulant group as compared to a nonanticogulant group of subjects tested several years ago despite the more rigid test conditions in the recent group. It is evident that anticoagulation does not appreciably alter the cerebrovascular (collateral) reserve as measured by electroencephalographic testing, although clinical symptoms may abate.

This idea was further substantiated by repetition of the electroencephalographic compression tests on a number of anticoagulated patients who were first evaluated three to four years before. Three-quarters showed equivalent electroencephalographic abnormality with the identical compression test. In one instance, a positive response occurred in a previously negative patient. It should be reemphasized that these patients had been treated by continuous anticoagulation therapy with clinical success.

To summarize the results from this small series:

1. The technic of carotid compression with electroencephalographic monitoring can be modified to provide a valuable index as to collateral reserve in the subject suspected of having intermittent vascular syndrome.

2. The technic can also be used as a laboratory aid in ruling out such a diagnostic possibility.

3. This method is most valuable in following the vascular status of an individual patient longitudinally, especially if the test is carried out by the same person.

4. Evaluation of anticoagulation therapy with this technic suggests that this treatment does not arrest the progression of the underlying arteriosclerotic process, although patients may be kept in clinical remission.

General discussion on electroencephalography, second session, May 1, 1960

Dr. Peritz Scheinberg, Chairman

DR. SCHEINBERG: Professor Gastaut, I am sure that almost everyone here would be very pleased to hear you add a brief discussion concerning the technic of rheoencephalography, since most of us are interested to know how this is done.

PROFESSOR GASTAUT: Rheoencephalography is a recording of the pulsatile changes in impedance of the brain. The concept of measuring the impedance of tissue with alternating current is an old one and has recently been elaborated for the brain by Jenkner. The technic of the examination consists of using the hemicranium as one arm of a Wheatstone bridge. Electrodes are placed over the frontal and mastoid regions, and alternating current, usually 1,000 cps, is passed between the electrodes. The bridge is balanced with a variable resistance so that no current passes between the 2 cranial electrodes. The balance of the bridge is then changed so that a small potential difference occurs between the 2 electrodes. The variation in this potential difference is recorded, and changes in it are related to changes in impedance which are apparently related to blood flow through the head. With each heart beat, the potential difference changes and a wave is recorded simultaneously with the electrocardiogram. Alterations in the recorded pattern of changes in impedance have been found with a variety of neurologic disorders, including subdural hematoma, hemispherectomy, stellate ganglion block, and brain tumor. You can find this matter discussed in the first meeting of the *Conference D'Electronic International*, the International Electronics Conference, held in Paris last year.

Another question is, "What part of this response is from the brain, and what is from the skull?"

We have operated on animals and are sure now that there is some skull response, but the chief information comes from the brain. There is no doubt about this because we have done control studies in animals with the rheoencephalograms done on the skull, from the brain, from the dura, from the cortex, and under the cortex. The results are quite clear, confirming that the most important part of the rheoencephalograms comes from the brain.

DR. SUGAR: You will find an article by Jenkner (*Confina Neurologica* 19:1, 1959) on this subject abstracted in the next *Year Book of Neurology and Neurosurgery*. In brief, this has to do with what looks like a pulse wave which is recorded by sending an alternating current through the cerebral hemisphere and recording the changes in the balance of a Wheatstone bridge from minute to minute. It does not go back to the older technics which required an opening in the head and attaching a direct plethysmograph to the hole. It is a very useful procedure as you heard from Professor Gastaut.

DR. WEISS: I have been asked a question: "What is the incidence of complications when the carotid is compressed?"

This can be a potentially dangerous procedure. However, when we do it with electroencephalographic and electrocardiographic monitoring, also measuring the blood pressure, the incidence of complications is markedly reduced because we can pick up any minor change as soon as it occurs and stop the pro-

cedure. Over a period of approximately four years, we have not had any serious complications using these technics. Occasionally, we see a focal motor seizure or subjective paresthesias in the side opposite the compressed artery. I have had one episode of cardiac arrest which, fortunately, turned out all right.

DR. WELLS: I have one question here which seems to be reasonably possible to answer: "Has anything fundamental about the origin and mechanism of electrical activity of the brain been learned from the study of cerebrovascular diseases?"

First of all, we have added some ideas about the functional capacity of the brain and particularly the appearance of slow waves or the absence of electrical activity. As Dr. Gastaut himself and workers at his laboratory have shown, hypoxia is associated first with the appearance of slow activity, usually in the theta range, whereas anoxia is associated with total absence of cerebral electrical activity, at least as recorded from the scalp. So we can get some idea of hypoxia as opposed to anoxia from looking at the brain waves in these situations.

One other very interesting observation seen in the presentation of Dr. Gastaut today, and I think in some earlier work of Dr. John Meyer, is that episodes which clinically closely resemble seizures with adversive and clonic movements, which we would expect to be characterized by spiking or paroxysmal activity in the scalp electroencephalogram, are found to be associated with electrical silence. This is reasonably good evidence that, when looking at a clinical episode, one cannot in any way predict whether this is associated with spiking or paroxysmal activity or whether there may not be electrical silence.

Anticoagulant therapy in cerebral thrombosis and cerebral embolism

A national cooperative study, interim report

C. Miller Fisher, M.D.

In the spring of 1958, representatives from the neurology divisions of 7 clinical centers in the United States began a study of the efficacy of long-term anticoagulation on cerebral ischemia and infarction caused by thrombosis and embolism. A cooperative approach was undertaken in an effort to reach a conclusion in the pressing matter of the management of occlusive cerebrovascular disease sooner than any one center could hope to accomplish it alone. The study was formed under the leadership and guidance of Dr. C. Miller Fisher of the Massachusctts General Hospital, Boston, who acted as chairman and director of the coordinating center at which records from the various participating units were evaluated. In addition, the participating physicians were John Broward, Jackson Memorial Hospital, Miami; Harry C. Fang and Robert N. Baker, University of California Hospital, Los Angeles; Sigmund N. Groch, Bellevue Hospital, New York City; Albert Heyman, Duke University Hospital, Durham, N. C.; Herbert R. Karp, Grady Memorial Hospital, Atlanta; and James F. Toole, University of Pennsylvania Hospital, Philadelphia. Professor Hugo Muench of the Harvard School of Public Health was statistical consultant to the project. Dr. Ellen McDevitt, Dr. R. D. Adams, and Dr. Irving S. Wright assisted in planning the study. Before initiation of the study, several organization meetings were held in order to reach agreement on definitions, terminology, method of procedure, and data sheets. This report includes data sent to the coordinating center up to December 1, 1959, approximately eighteen months from the initiation of the study.

Methods of case selection and treatment

All the patients in this study were divided into 5 diagnostic categories:

1] **Transient ischemic attacks (TIA).** This refers to the occurrence of single or multiple episodes of cerebral dysfunction lasting no longer than one hour and clearing without significant residuum. They are extremenly varied in symptoms, signs, duration, and frequency. The effect of anticoagulants in this group was analyzed in terms of their modifying the frequency or severity of attacks, as well as preventing the development of persistent neurologic deficits.

2] **Thrombosis-in-evolution.** This category includes patients in whom a neurologic deficit was developing in a step-wise, progressive fashion. The effectiveness of anticoagulants in this group was measured in terms of preventing further advancement of the stroke or decreasing the incidence of associated or subsequent transient ischemic attacks.

3] **Thrombosis.** This group includes patients with one or more recent episodes of cerebral infarction in whom the neurologic deficit was stable at the time they entered the study.

4] **Cerebral embolism.** This category includes patients with cerebrovascular disease in whom a likely source of emboli was present and whose clinical history supported the diagnosis.

5] **"Thorem."** In this group, the differentiation between thrombosis and embolism could not be made with certainty. Such cases were designated as "thorem" (a contraction of *th*rombosis *or em*bolism).

Only patients whose last cerebrovascular episode had occurred within eight weeks be-

fore randomization were admitted to the study.

Almost all of the patients in the study were selected from the hospital wards and were not private cases. Once a patient was assigned to one of the above categories, he was considered a candidate for anticoagulation therapy provided an examination of the stool, urine, and cerebrospinal fluid failed to reveal any evidence of bleeding. In addition, the feasibility of long-term outpatient anticoagulation therapy was considered from the standpoint of the patient's geographic location as well as his ability to understand treatment instructions and to return frequently for follow-up observation. Evidence of an active peptic ulcer, serious intercurrent illness, bleeding diathesis, sepsis, collagen disease, endocarditis, or mental disease was considered a contraindication to anticoagulant therapy. Patients were not excluded from the study because of hypertension or diabetes. When suitability for the study had been determined, patients were assigned to the treatment or control group on a statistically random basis by means of sealed envelopes.

If the patient's last cerebrovascular episode had occurred less than seven days before his assignment in the treatment group, he was given Dicumarol and heparin. Dicumarol alone was used if the episode occurred more than seven days previously. Heparin was administered intravenously in dosages of 50 mg. every four hours until Dicumarol had reduced the prothrombin activity to therapeutic range (15 to 25% of normal). If the patient was unable to swallow, Coumadin was administered parenterally. The Lee-White clotting time was determined once a day to ensure that anti-

TABLE 1

CHARACTERISTICS OF THE CONTROL AND TREATED GROUPS

		Transient ischemic attacks		*Thrombosis-in-evolution*		*Thrombosis*		*Thorem*		*Embolism*		*Total*	
		C	*T*	*C*	*T*	*C*	*T*	*C*	*T*	*C*	*T*	*C*	*T*
Number of cases		15	17	51	49	50	68	54	48	14	14	184	196
Sex	Male	9	14	28	25	35	55	34	26	7	6	113	126
	Female	6	3	23	23	15	13	20	22	6	8	70	69
Color	White	14	16	34	31	38	55	45	34	13	9	144	145
	Negro	1	1	16	17	12	11	9	14	1	5	39	48
Age	Under 55	1	2	7	7	11	14	8	6	1	3	28	32
	55 and over	14	15	43	41	39	54	45	42	13	11	154	163
Blood pressure	150/90 or less	4	5	17	17	21	32	14	14	7	7	63	75
	150/90–180/100	7	8	15	17	17	18	22	9	3	3	64	55
	180/100–210/115	2	3	16	10	6	8	9	18	2	3	35	42
	Over 210/115	2	0	1	4	6	7	6	6	1	0	16	17
Territory	Internal-middle carotid	8	10	30	25	36	55	48	45	13	13	135	148
	Vertebral-basilar	6	6	18	22	11	11	6	2	1	1	42	42
	Unknown	1	1	3	2	3	2	0	1	0	0	7	6
Rating at randomization (0–10)	Above 5	10	10	32	20	26	37	17	20	5	6	90	93
	5 and below	0	0	19	27	23	30	36	28	9	8	87	93
Time since last neurologic event	7 days or less	10	11	40	36	28	38	43	35	13	13	134	133
	Over 7 days	5	6	11	13	22	29	11	13	1	1	40	61
Previous stroke		1	2	7	8	11	16	5	11	2	4	26	41
Smoker		6	7	21	20	25	48	19	16	3	4	64	95

coagulant activity had been achieved. The prothrombin activity was determined daily during hospitalization and at one- to two-week intervals after discharge. Most of the laboratories in the study used the one-stage Quick method with Simplastin reagent. When hemorrhagic complications occurred, every effort was made to control the bleeding, and, when possible, anticoagulation therapy was reinstituted.

Other than the fact that control patients were given a placebo capsule, the management of the two groups was similar. Hypotensive drugs, low-fat diet, or changes in smoking and work habits were avoided in both groups of patients when possible. In the follow-up period, both control and anticoagulant patients returned at the same intervals for evaluation of their clinical status.

CASE MATERIAL AND METHODS OF RATING

Table 1 presents an analysis of the control and treated groups in regard to sex, color, age, degree of hypertension, cerebrovascular territory involved, severity and duration (more or less than seven days) of the neurologic event at randomization, occurrence of previous strokes, and smoking habits. The degree of initial neurologic and general disability was rated on a scale from 0 (death) to 10 (normal) and formed the basis for measuring the patient's improvement or worsening after randomization. It will be seen that, in most respects, the 2 groups were remarkably comparable. The age of the patients was arbitrarily divided into those less than or more than 55 years. The degree of hypertension was based on an average of a number of blood pressure readings in each patient and was rated as follows: I=average blood pressure, 150/90 mm. Hg or less; II=150/90 to 180/100; III=180/100 to 210/115; and IV=more than 210/115. The relative number of cases involving internal carotid and vertebral-basilar systems varied from category to category, and, in the whole series, the comparative totals were 283 (77%) in the carotid system and 84 (23%) in the vertebral-basilar system.

To determine the effect of anticoagulants, the cases were analyzed as to the incidence of [1] deaths, [2] transient ischemic attacks, [3] progression of neurologic deficits due to either extension of the infarcted area or a new in-

TABLE 2
RESULTS OF THERAPY IN ALL CATEGORIES

Category	Number of cases		Patient-months		Deaths total		Deaths due to anticoagulations		Neurologic events										Cause of death									
									Transient ischemic attacks				Progression due to infarction															
									Number of patients with attacks		Total number attacks		Number of patients		Number early worsenings		Number late worsenings		Progression due to cerebral hemorrhage		Extracerebral thromboembolism		Brain infarction		Brain hemorrhage		Other hemorrhage		Cardiac		Misc.		Unknown	
	C	T	C	T	C	T	C	T	C	T	C	T	C	T	C	T	C	T	C	T	C	T	C	T	C	T	C	T	C	T	C	T
Transient ischemic attacks	15	17	127	156	1	1	0	0	11	5	§670	§20	3	1	0	0	3	1	0	0	1	0	1	7	4	0	0	0	0	0	1	0	0	0	0	0
Thrombosis-in-evolution	49	51	364	294	10	9	0	2	3	1	§16	3	14	7	11	6	9	1	0	1	2	1	7	4	0	1	0	1	1	1	1	2	1	0		
Thrombosis	48	64	375	360	6	12	0	4	5	1	§10	§3	6	6	2	3	6	3	0	0	4	0	3	5	0	2	0	2	0	0	0	1	3	2		
Thrombi	55	48	319	252	12	7	0	2	0	3	0	3	3	5	0	2	4	4	0	1	1	1	9	1	0	0	2	0	1	1	1	1	2	2		
Emboliem	15	15	58	42	8	9	0	0	0	0	0	0	1	2	1	2	0	0	0	0	2	1	7	6	0	0	0	0	1	1	0	0	2	2		
Totals	182	195	1,243	1,104	37	38	0	8	19	10	§596	§29	27	21	14	13	22	9	0	2	9	3	27	16	0	3	0	5	2	4	2	4	6	6		

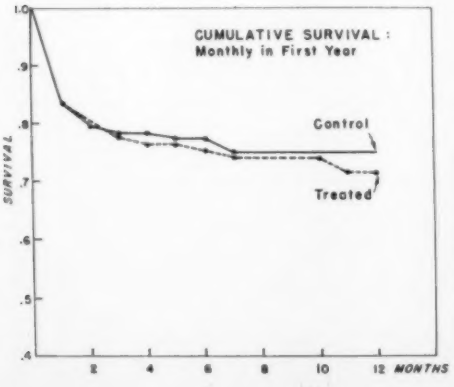
Gross mortality per 1,000 patient-months { → Control: 29.7 Treated: 34.4 → Subtracting fatal hemorrhagic complications → Control: 29.7 Treated: 27.1

TABLE 3

MORTALITY BY MONTHS FOR FIRST YEAR OF STUDY (TIA GROUP EXCLUDED)

Month		*Thrombosis-in-evolution*		*Thrombosis*		*Thorem*		*Embolism*		*Totals*	
		No. of Patients	*Deaths*	*No. of Patients*	*Deaths*	*No. of Patients*	*Deaths*	*No. of Patients*	*Deaths*	*No. of Patients*	*Deaths*
First	C	49	7	47	2	55	10	15	7	166	26
	T	52	5	64	10	48	5	16	6	180	26
Second	C	39	1	42	1	36	2	6	1	123	5
	T	32		40		30	2	5	2	107	4
Third	C	33		37	2	31		5		106	2
	T	29		36	2	26	1	3		94	3
Fourth	C	33		30		30		4		97	
	T	26		34		23	1	3		86	1
Fifth	C	31		28		29	1	4		85	1
	T	23		32		17		3		75	
Sixth	C	28		26		25		3		82	
	T	22		31	1	17		2		72	1
Seventh	C	23	2	24		24		3		74	2
	T	18	1	23		15		2		58	1
Eighth	C	22		23		17		3		65	
	T	17		21		12		1		51	
Ninth	C	18		21	1	14		2		58	1
	T	16		18		11		1		46	
Tenth	C	16		20		12		2		50	
	T	14		15		11		1		41	
Eleventh	C	15		19		10		2		46	
	T	13	1	12		9		1		35	1
Twelfth	C	14		15		8		2		39	
	T	10		7		8		1		26	

farction, and [4] the advent of extracerebral thromboembolism, such as myocardial infarction, pulmonary embolism, or limb ischemia. The interpretation of transient neurologic phenomena was most difficult, especially of such symptoms as dizziness with changes in posture, increased numbness and tingling in an area with persistent sensory deficit, slight staggering, and minor epileptic seizures. Accordingly, such episodes were considered as only questionable evidence of transient cerebral ischemia and were not included in the tabulated data. Progression of neurologic deficits or the development of new signs of cerebral infarction was classified as *early* if it appeared within two weeks after randomization and *late* if it appeared after this period.



EXCLUSION OF CASES AFTER RANDOMIZATION

After randomization, 25 cases were dropped from the study for a variety of reasons: [1] patients dying within twenty-four hours after randomization, that is, before Dicumarol could have had any therapeutic or toxic effect; [2] patients randomized before complete laboratory evaluation and later found to have evidence of bleeding; [3] patients selected for anticoagulant therapy but who for reasons of oversight did not receive this form of treat-

ment; [4] patients having cerebral complications of carotid arteriography; [5] patients with brain tumor, brain abscess, or other nonvascular cerebral conditions who were included erroneously. These patients were excluded from the study unless anticoagulation had been used with deleterious effect.

In at least 2 instances, anticoagulants were administered to patients with intracerebral hemorrhage. Both patients died, and these cases were retained in the study; 3 patients in the control group also had an intracerebral hemorrhage. These patients were excluded from the study although they subsequently died. In all probability, other misdiagnosed cases have been enrolled in the study, but it is expected that they would be equally represented in the control and treatment groups. Patients in whom anticoagulants were stopped within two weeks before their deaths were counted as deaths while on anticoagulants.

RESULTS

Table 2 summarizes the deaths and cerebrovascular events following randomization in both the treated and control subjects. There

TABLE 4
SITE AND SEVERITY OF HEMORRHAGIC COMPLICATIONS

Site	*TIA*				*T-in-E*				*Thrombosis*				*Thorem*				*Embolism*				*Total*
	Fatal	*Severe*	*Moderate*	*Mild*	*Fatal*	*Severe*	*Moderate*	*Mild*	*Fatal*	*Severe*	*Moderate*	*Mild*	*Fatal*	*Severe*	*Moderate*	*Mild*	*Fatal*	*Severe*	*Moderate*	*Mild*	
Upper gastrointestinal		1						3	2	1	1	1	1	1							11
Lower gastrointestinal						1		3		1	3	3			2	1					14
Urinary			1				6				6	2			3	2			2		22
Intracranial					1				2					2							5
Nasal							2									2					4
Skin												2				1					3
Miscellaneous																					19
Hemarthrosis			1																		
Scalp laceration					1																
Muscle							1					1									
Retinal artery occlusion with hemorrhage							1														
Gums								1							1						
Dental										1		1									
Decubitus ulcer											1										
Vaginal												1		1							
Oral												1								1	
Hemoptysis												1									
Bilateral adrenal hemorrhage											1		1								
Subconjunctival																1					
External ear canal																1					
																					78

were 37 deaths among the 182 control patients compared to 38 among the 195 patients receiving anticoagulants. The treated patients were followed for a shorter period of time, and the mortality per 1,000 patient-months was 29.7 in the control series and 34.4 in the treated group. Hemorrhagic complications of anticoagulant therapy caused 8 deaths, and, even if these were allowed for and subtracted from the deaths in the treated group, the difference in the mortality rates is still not significant (control 29.7 and treated 27.1 per 1,000 patient-months). The cumulative survival curves were almost parallel in the 2 groups during the first year (see figure). Table 3 shows the mortality rate in each diagnostic category month by month. The majority of the deaths (61 of 75 cases) occurred in the first two months after randomization.

In the category of *transient ischemic attacks*, it will be noted that 11 of the 15 patients in the control group continued to have cerebral ischemia in contrast to 5 of the 17 patients in the treatment group. Of the control subjects who continued to have frequent attacks, 2 received anticoagulants one month after randomization and were removed from the study at that point. After randomization, the total number of transient ischemic attacks in the control group was considerably higher than in the treated group. While the exact number of such episodes is often difficult to estimate in patients with very frequent attacks, it would appear that 500 to 600 ischemic attacks occurred in the control patients in contrast to approximately 20 attacks in the treated patients. Persistent neurologic deficits occurred in 3 patients in the control group and only 1 in the anticoagulation group, all of which appeared more than two months after randomization. There was 1 death in each group with transient ischemic attacks.

In the category of *thrombosis-in-evolution*, 10 of the 49 control patients died compared to 9 of the 51 treated patients. In the control group, 14 patients had definite progression of neurologic deficits due to infarction as compared to 7 in the treated group. In addition, 1 of the treated patients worsened as the result of a cerebral hemorrhage. In the 14 control patients who had worsening of their neurologic deficits after randomization, there were a total of 20 episodes of progression or recurrent cerebral infarction, 11 early and 9 late. In the 7 treated patients, there were but 8 episodes of a progressive nature, 6 early and only 2 late.

Of the patients with *thrombosis and "thorem"* (considered as 1 group), 18 among the 113 controls and 19 among the 112 receiving treatment died. Of the latter, 6 died of hemorrhagic complications. Progression of neurologic deficits due to extension of the infarcted area or to a new cerebral infarction occurred in 9 of the controls and 12 of the treated patients, including 1 case of cerebral hemorrhage. The total number of episodes of worsening and the time of their occurrence in these 21 patients were approximately the same in both the control and the treatment groups.

In patients with *cerebral embolism*, anticoagulation failed to influence either the progression of the cerebrovascular disorder or the number of deaths. The mortality in the 30 patients in this group was extremely high, with all the 17 deaths occurring within two months after randomization.

The number of patients with early worsening of the neurologic deficit in all the diagnostic categories was approximately the same in the control and treated groups (14 and 13 patients, respectively). However, it is noteworthy that the incidence of late progression or recurrence of cerebral infarction in all categories was considerably higher in the control patients (22 cases) than in the treated patients (only 9 cases), indicating perhaps that anticoagulation may reduce the number of recurrent cerebral infarcts after the first two weeks of therapy.

Extracerebral thromboembolism occurred in 9 of the control patients and only 3 of those treated. Most of these cases were thought to represent myocardial infarctions, but few postmortem studies were made.

In all diagnostic categories, the progression of neurologic deficits or recurrence of cerebral infarction did not appear to be clearly related to inadequate anticoagulation. Of interest is the fact that 54 of the 58 patients with new or extension of the previous cerebral infarction had manifestations in the same cerebrovascular territory that was affected at the time of randomization. In other words, infarction ap-

TABLE 5
HEMORRHAGIC COMPLICATIONS ANALYZED ACCORDING TO BLOOD PRESSURE IN PATIENTS RECEIVING ANTICOAGULANTS

	Blood pressure	*Transient ischemic attacks*	*Thrombosis-in-evolution*	*Thrombosis*	*Thorem*	*Embolism*	*Total Number*	*%*
No complications	150/90 or less	4	13	22	12	7	58	44
	150/90–180/100	8	11	10	8	3	40	30
	180/100–210/115	2	6	4	10	3	25	19
	Over 210/115	0	3	3	2	0	8	6
						Total	131	99
Complications	150/90 or less	0	4	8	2	0	14	25
	150/90–180/100	0	7	6	1	0	14	25
	180/100–210/115	2	3	4	7	1	17	31
	Over 210/115	0	1	4	4	1	10	18
						Total	55	99

peared to occur or progress in the part of the brain already involved and not in another area of the cerebral circulation.

The possible effect of anticoagulant therapy on residual neurologic deficits was determined in an analysis of 20 consecutive control patients and 30 treated patients. All of them had an initial neurologic deficit rating of 5 or less, and none suffered any further infarction during the observation period. Six months after randomization, the control group had somewhat more neurologic deficit with an average rating of 3.5 compared to 4.3 in the treated group. However, this difference was not thought to be significant.

Conclusions regarding anticoagulant therapy. Long-term anticoagulation therapy does not appear to reduce the mortality in occlusive cerebrovascular disease and, indeed, is associated with an added risk of death due to the hemorrhagic complications.

TABLE 6
BLOOD PRESSURE IN 16 FATAL OR SEVERE HEMORRHAGIC COMPLICATIONS

Blood pressure	*Number*	*Per cent*
150/90 or less	3	19
150/90–180/100	3	19
180/100–210/115	6	37
Over 210/115	4	25
Total	16	100

The number of transient cerebral ischemic attacks is reduced by anticoagulation. However, both control and treated patients with transient cerebral ischemic attacks showed so few instances of cerebral infarction that no definite conclusions can be made regarding the value of long-term anticoagulation in this disorder.

The incidence of late cerebral infarction was reduced in patients with thrombosis-in-evolution, but the significance of this cannot be stated at present.

Hemorrhagic complications. Table 4 shows the site and severity of hemorrhagic accidents in the anticoagulant group according to the 5 categories. A total of 78 hemorrhages occurred in a period of 1,104 patient-months, or 1 hemorrhagic complication per 14 patient-months. In the following analyses, the numbers vary because pertinent data are lacking in some cases.

There were 8 fatal complications: [1] severe cerebellar ataxia and fall on sidewalk, with resultant fatal hemorrhage from scalp laceration, normal blood pressure, prothrombin activity 27%; [2] original stroke was hemorrhage—included in series by error—fatal second cerebral hemorrhage in first month, grade 4 hypertension, prothrombin time 47 sec.; [3] fatal intracerebral hemorrhage in third month, grade 2 hypertension, prothrombin activity in 11.1%; [4] fatal upper gastrointestinal hemorrhage at sixteen months, grade 2 hypertension, pro-

thrombin time 28 sec. (13%), radiologic evidence of duodenal ulcer five years previously; [5] fatal gastrointestinal hemorrhage (suspect) at two weeks, grade 4 hypertension, prothrombin time 41.6 sec.; [6] intracranial bleeding resulting from a dose of 75 mg. of Coumadin rather than Dicumarol; [7] fatal upper gastrointestinal hemorrhage at one month, grade 4 hypertension, prothrombin activity 2%; [8] unusual bilateral adrenal hemorrhage on eighth day, grade 3 hypertension, prothrombin activity 11% (anticoagulant not given according to protocol).

In addition, there were 8 severe hemorragic complications: [1] rectal bleeding to hypotensive levels in second week, grade 2 hypertension, prothrombin activity not known accurately; [2] bleeding from decubitus ulcer contributing to death; [3] severe upper gastrointestinal hemorrhage on tenth day; [4] hemorrhage from dental extraction, grade 2 hypertension, prothrombin time 71 sec.; [5] lower gastrointestinal hemorrhage, normal blood pressure, prothrombin time 75 sec.; [6] severe gastrointestinal hemorrhage, grade 3 hypertension, prothrombin time not known; [7] severe upper gastrointestinal hemorrhage plus possible intracerebral hemorrhage, grade 3 hypertension, prothrombin activity 150 sec.; [8] subarachnoid hemorrhage with temporary coma, grade 3 hypertension, prothrombin activity 27%.

In order to determine the relation of hemorrhagic complications to the height of the blood pressure, the anticoagulant patients were divided into 2 groups, those with bleeding accidents and those without; the 2 groups were then analyzed with respect to the blood pressure levels. The results are presented in Table 5, which shows that patients with grade 3 and 4 hypertension (that is, higher than 180/100) comprised 49% of the group with complications and only 25% of the group without complications. There would seem to be little doubt, therefore, that hypertension contributed to the frequency of hemorrhagic complications in our patients. Furthermore, of the 16 patients with fatal and severe bleeding accidents, 3 had normal blood pressure, 3 were slightly hypertensive, and 10 (62%) had grade 3 or 4 hypertension (Table 6).

However, if the patients with hemorrhagic complications are analyzed according to blood pressure and level of the prothrombin activity at the time of bleeding, it is found that, *regardless of the blood pressure*, 47 of 54 hemorrhagic accidents occurred at a prothrombin level of 15% or less (Table 7); 34 occurred with a prothrombin activity of less than 10%, another 13 occurred at a level between 10 and 15%, and only 7 occurred above 15%. These data suggest that the lowest prothrombin level that is safe is about 15% rather than 10%, as is widely recommended. Provided that the prothrombin level is maintained above 15%, anticoagulation is no more dangerous in hypertensive patients than in normotensives.

Complications were slightly more frequent in females, who comprised 44% of the group with bleeding accidents and only 30% of the nonbleeding group.

The time at which hemorrhagic accidents

TABLE 7
RELATION OF HEMORRHAGIC COMPLICATIONS TO PROTHROMBIN LEVEL AND BLOOD PRESSURE

	Prothrombin	*Fatal*	*Severe*	*Moderate*	*Mild*	*Total*
Elevated blood pressure	Above 15%		1	2		3
	10–15%	2		5	5	12
	Below 10%	3	2	13	5	23
	Total	5	3	20	10	38
Normal blood pressure (150/90 or less)	Above 15%	1		1	2	4
	10–15%			1		1
	Below 10%	1	1	6	3	11
	Total	2	1	8	5	16

occurred varied greatly: first month, 22; second month, 12; third month, 5; fourth month, 13; fifth and sixth months, 7; seventh to ninth months, 5; tenth to seventeenth months, 7. The fatal and severe hemorrhages occurred as follows: first week, 2; second week, 3; second to fourth weeks, 3; second to fourth months, 6; fifth to seventh months, 1; later, 1.

Only 6 of the hemorrhages were attributable to intravenous heparin therapy—2 with coffee-ground vomitus and 4 with moderate hematuria. This low incidence is remarkable in view of the fact that many of the patients were extremely ill, and hypertensive patients were not excluded from the series.

The cases of gastrointestinal hemorrhages were analyzed to determine whether bleeding tended to occur early after randomization with good control and at a later time with poor control, but no reliable trend was discerned. In nearly all patients with upper gastrointestinal bleeding, intensive inquiry revealed a history of peptic ulceration or distress.

There were 8 hemorrhagic complications in the control group: 3, moderate hematuria; 1, coffee-ground vomitus; 1, bright red rectal bleeding; 1, severe gastrointestinal hemorrhage; 1, ten-minute hemoptysis; 1, dependent purpura.

EARLY NATURAL HISTORY OF NONHEMORRHAGIC CEREBROVASCULAR DISEASE

Since one-half of our patients were selected at random to receive no special therapy, instructive information has accumulated concerning the natural history of a relatively unselected group of patients with cerebral ischemia.

Transient ischemic attacks (TIA). The 15 patients in this group will be tabulated and the events before and after randomization compared.

Before randomization	*After randomization*
1. Occasional attack of left-sided weakness and numbness	4 attacks in next year
2. 2 mild strokes in basilar territory—dizziness, diplopia, weakness, and numbness of the left arm and leg, followed by TIA characterized by loss of equilibrium, falling away of left side (2 per week for seven months)	4 attacks in next year
3. 40 TIA in two months lasting fifteen to sixty minutes (5 per week), bilateral weak legs, dim vision, weak right arm, diplopia, dysarthria, dysphagia, roaring in head	3 attacks in next year
4. For three months, attacks 1 to 3 per week of weak, numb, left hand, pain behind right eye	13 attacks in three months, then had left hemiparesis
5. 16 attacks in three days lasting fifteen to twenty minutes, of weak right arm and numbness of right arm and garbled speech	10 attacks in next three weeks and no further events in next twenty months
6. In eighteen days, 33 attacks of right amblyopia and weakness of left arm, lasting one to thirty minutes	80 attacks in next year with slight deficit accruing
7. In four months, 150 to 200 attacks of blurred vision, object slanted, diplopia, prickling of tongue lasting two to fifteen minutes, pulsating noise in left ear	3 to 12 attacks daily for one month, then 3 attacks of deep coma lasting up to seventy minutes, anticoagulant begun (no further attacks)
8. 16 attacks in five months of lightheadedness, eyes deviated to left, legs weak, diplopia, dysarthria	Attacks daily for next twenty-eight days when local physician placed him on anticoagulants (no further spells)
9. For six months, episodes, 2 per week, of weakness and numbness of left face, arm, and leg, lasting five to thirty minutes; speech thick, left facial droop	3 to 6 attacks per week for ten months, then cessation
10. 2 episodes left hemiplegia four weeks apart, then transient blindness right eye for ten minutes	4 attacks in next four months

Before randomization	*After randomization*
11. 6 attacks in three days of sparkling lights before right eye associated with weakness of left hand and speech disturbance	No attacks in next two months, then had edema of legs and shortness of breath, found quadriplegic in coma and died after drastic diuretic therapy
12. 2 episodes in one day of numb ear, arm, and leg, lasting one-half hour	No recurrence in one year
13. In two weeks, 4 to 5 episodes of giddiness, nausea, vomiting, visual blurring lasting less than one minute	No attacks in next three months
14. 2 attacks of left hemiparesis four hours apart lasting thirty minutes	No recurrence in nine months
15. 4 attacks in one month of dizziness, wall slanted, dysarthria	Spells continued about 1 per week for six months (? reliability)

These data clearly illustrate the great variability in the course of patients with transient ischemic attacks. This fact must always be taken into consideration in interpreting the results of therapy, whether it be medical or surgical.

Thrombosis-in-evolution. Of the 41 patients examined during the intermittent development of a stroke, 12 showed worsening in the next two weeks (roughly 30%); 27 were in the internal carotid artery (ICA) group with 7 events and 14 in the vertebral-basilar (VB) group with 5 events.

Of the 41 patients, 31 were followed for six months or more (23 ICA and 8 VB). There were 7 late deteriorations (that is, after two weeks), 4 in the ICA group and 3 in the VB group. The late impairments occurred at two, five, eight, eleven, twelve, sixteen, and eighteen months, respectively, and all were in the vascular territory originally affected; 4 patients had both early and late worsening.

Thrombosis. Of the 42 cases in this group, 29 were internal carotid, 11 vertebral-basilar, and 2 unknown. Only 3 worsenings were seen in the two-week period after randomization, 2 in the ICA group and 1 in the VB group. A complete neurologic deficit was noted in 11 patients when they were randomized, and the others ranged from a severe deficit to almost normal; 21 patients entered the series within seven days of the ictus.

Of the 42 patients, 31 were followed for six months or more (22 in the ICA group, 1 VB, and 1 unknown). Late worsening was seen in 6 patients, 3 once (two, four, and six months) and 3 twice (two and three, two and three, and four and seven months, respectively); 5 were in the ICA group, and 1 was in the VB group.

All worsenings, early and late, involved the same territory initially affected, and no new stroke developed; 3 patients died late, 1 at two months of suspected myocardial infarction, 1 at three months of undetermined cause, and 1 of debility at nine months.

"Thorem." Of the 41 cases in this group, 37 were internal carotid and 4 vertebral-basilar. Only 1 worsening occurred in the two-week period after randomization, in an internal carotid case; 11 of the patients had a complete neurologic deficit initially, and 27 entered the series within seven days of the ictus.

Of the 41 patients, 27 were followed for six months or more (24 ICA and 3 VB). There were 1 late worsening (six months) and 1 questionable late worsening (two months); 3 died, 2 of pneumonia at one and one-half months and 1 of undetermined cause at three months.

In the thrombosis and "thorem" groups combined, there were 83 cases with 4 early worsenings (5%), 8 late worsenings (9%), and 6 deaths. It would appear that these were relatively inactive groups in the year or so after randomization.

BRIEF ACCOUNT OF NEUROLOGIC EVENTS AND DEATHS AFTER RANDOMIZATION

Transient ischemic attacks

Neurologic events in 11 control patients:

1] Occasional attacks of numbness and weakness of left side lasting a few minutes, recurring for twelve months

2] Occasional dizziness, imbalance, and numbness for five months, then cessation

3] Occasional weakness and ataxia for two months, then cessation

4] Occasional attacks of numbness and weakness of left hand and pain behind right eye for three months, then left hemiparesis developed

5] 10 attacks of numbness and weakness of the left hand in ten days, then cessation for nineteen months

6] Repeated attacks of blindness in the right eye and/or weakness and numbness of the left arm 5 to 10 times monthly for sixteen months

7] 3 to 12 attacks daily for one month of blurred vision, dizziness, objects slanted, vomiting, prickling of tongue; attacks lasted progressively longer, and, finally, patient had 3 episodes of deep coma lasting up to seventy minutes—removed from study and anticoagulants given with no further attacks

8] 20 attacks in one month of deviation of eyes to the left, lightheadedness, diplopia, weak legs, weak left grip; family physician intervened and administered anticoagulants, and attacks ceased

9] 2 to 3 attacks weekly for ten months of numb face, thick speech, dropped things, one leg crumpled—then cessation

10] One attack monthly of blindness in the right eye and loss of control of left hand

11] Patient suddenly became quadriplegic and comatose three months after randomization and died after drastic diuretic therapy.

Treated (5 patients):

1] One attack of dizziness and weakness of extremities lasting a few minutes

2] One attack of transient monocular blindness on day after randomization

3] One mild dizzy spell at two months

4] In third month after randomization, patient had daily for one week 1 to 2 spells of numbness of right hand and weakness of one side of the face; no recurrence in seven months

5] Several episodes of right hemiplegia on day before randomization, then eight hours after receiving heparin had persistent right hemiplegia with good recovery in succeeding months.

Patients in the control and treated groups who had further attacks or worsenings did not differ significantly from the entire group in regard to age, sex, vessel involved, blood pressure, and smoking habits.

Deaths—Control: see patient 11 above. *Treated:* Patient 1 died in congestive heart failure at thirteen months.

Thrombosis-in-evolution

Neurologic events in 17 control patients:

1] Severe brain stem signs became slightly worse one day after randomization; after uneventful course for thirteen months, dizziness was followed by persistent gait difficulty

2] Several attacks of blindness in right eye, numbness of left leg, and left facial weakness after ten to fourteen months

3] Additional brain stem signs after seven months; after thirteen months, full basilar thrombosis deficit developed with death in three days

4] Moderate weakness of left arm became complete plus homonymous hemianopsia on seventh day; left leg became completely paralyzed at fifteen months

5] Moderate right hemiparesis worsened on fourth day; another stroke at eighteen months, details not known

6] Severe basilar deficit became worse day after randomization

7] Mild worsening of basilar stroke after twelve months (dim vision)

8] Episode of diplopia and pain in face at one and one-fourth months

9] Left hemiparesis became worse one day after randomization, then improved; left hemiparesis recurred at two months and persisted

10] Right hemiparesis after initial recovery recurred and persisted at two months

11] Moderate basilar deficit became much worse on third day, and private physician administered anticoagulants

12] 9 attacks of weakness and numbness of right arm and leg in first month

13] Left hemiparesis became complete in two days, and patient died on eighth day

14] Moderate left arm weakness became much worse in first week, improved, but five months later paralysis recurred and persisted

15] Right hemiparesis became much worse on fourth day

16] Moderate basilar paralysis became total, and death occurred on eighth day

17] Moderate worsening of basilar paralysis after one week.

Treated (9 patients):

1] Left hemiparesis became total paralysis on first day

2] Severe stroke possibly worsened on second day with death (not given anticoagulant exactly according to protocol)

3] Became slightly dysarthric and less responsive for twelve hours in tenth month

4] Brain hemorrhage included by error, suffered another cerebral hemorrhage at one month with death (prothrombin activity 47 sec.)

5] Moderate basilar paralysis became total quadriplegia with death after one month

6] Moderate basilar syndrome, became totally quadriplegic with death at three weeks

7] 2 or 3 thirty-minute episodes of dysphagia and thick speech at six months

8] Moderate lateral medullary infarct became

slightly worse, and patient died unexpectedly on third day, having been satisfactory a few minutes before

9] Slight worsening of right hemiparesis on first day.

An analysis of those patients whose condition worsened showed no significant diagnostic characteristic compared with the total group. There may have been a greater tendency to worsening in males, whites, and those with a more severe initial deficit, but no significant difference could be established. There was no relation to blood pressure, vascular territory, or a previous stroke.

Deaths–Control (10 patients):

1] Died in one month of severe paralysis and pneumonia

2] See patient 3 above

3] Died of severe paralysis and pneumonia on third day

4] Death from increasing cardiac failure in three weeks

5] Death with severe paralysis in six months

6] Death from undetermined cause at two months

7] See patient 13 above

8] See patient 16 above

9] Death with severe paralysis in twelve hours

10] Bedridden, death from pyelonephritis at seven months

Treated (9 patients):

1] Fell on sidewalk at four months with fatal hemorrhage from scalp laceration

2] See patient 4 above

3] Died of carcinoma of lung at eleven months

4] Died in nine days with rising nonprotein nitrogen and stupor; heparin omitted by error on second, third, and fourth days–autopsy showed superior cerebellar artery infarction of moderate size

5] Died in two days with severe paralysis

6] See patient 5 above

7] See patient 6 above

8] Death from myocardial infarction at seven months

9] See patient 8 above.

Thrombosis

Neurologic events in 10 control patients:

1] 2 brief attacks of numbness of fingers at two months

2] 3 attacks of numbness of the right limbs at four months

3] Diplopia, thick speech, nausea, and vomiting for one hour at three weeks

4] Occasional perioral numbness, vertigo, and ataxia

5] Thirty-minute attack of aphasia and weak right hand at four months; moderate aphasia developed at seven months

6] Right hemiparesis and aphasia developed at six months

7] Weak, numb left leg at two months; 50% weakness of left arm and leg at three months

8] Right hemiparesis became worse on second day

9] Marked worsening of right hemiparesis on second day

10] Right hemiparesis and aphasia developed at one month; blindness in left eye at two months.

Treated (7 patients):

1] Moderate increase in right hemiparesis at thirteen months

2] Severe stroke on opposite side at six months

3] Worsening of left hemiparesis on fifth day; anticoagulants not given exactly according to protocol

4] Severe hemiplegia developed at one month

5] Severe progression of moderate basilar paralysis to quadriplegia and death

6] A few episodes of tingling in cheek

7] Superior cerebellar artery syndrome progressed to coma and death in three days.

Those in whom worsenings occurred were compared with the total group in regard to color, sex, age, blood pressure, territory involved, previous stroke, rating at randomization, and smoking habits, and the 2 groups did not differ appreciably.

Deaths–Control (6 patients):

1] Died suddenly at two months (possible myocardial infarction)

2] Severe paralysis, died of debility at nine months

3] Severe stroke, died in coma on fourth day

4] Severe stroke, died of infection at three weeks

5] Died of undetermined cause at four months

6] Died suddenly at two and one-half months (possible myocardial infarction).

Comment: Only 3 patients died of their neurologic disease.

Treated (12 patients):

1] Died of intracerebral hemorrhage at three months

2] Died in diabetic coma on fifth day

3] Died suddenly at three months (possible myocardial infarction)

4] Severe paralysis, died of pneumonia in three weeks

5] Died of severe upper gastrointestinal hemorrhage at sixteen months

6] Died of possible gastrointestinal hemorrhage at two weeks

7] Severe paralysis, died of pneumonia on eighth day

8] Severe paralysis, died of debility in two months

9] See patient 5 above

10] Died of intracranial bleeding after toxic dose of Coumadin

11] See patient 7 above

12 Sudden unexepected death on third day (possible aspiration pneumonia).

Thorem

Neurologic events in 3 control patients:

1] Slight increase in weakness of left arm at one month; recurrence of hemiparesis at six months

2] Mild weakness of arm at one month

3] "Deteriorated neurologically." Comment: The worsenings in the control group were not severe.

Treated (8 patients):

1] Ataxia and weakness for one hour at two months, pain and weakness in legs for one week at seven months; confusion and weak legs for three hours at nineteen months

2] Coma for one-half hour related to hypotensive agents on sixth day

3] Onset of hemiplegia at three and one-half months when prothrombin time was 150 sec.

4] Found comatose with bloody cerebrospinal fluid at four mouths

5] Transient recurrence of hemiparesis at seven months

6] Moderate weakness of arm increased to paralysis on second day

7] Mild sensory deficit added to hemiparesis at three weeks

8] Went into unexplained hypotensive shock on tenth day, became stuporous, and died.

No clinical characteristics separated those who fared poorly from the group as a whole.

Deaths–Control (12 patients):

1–9] 9 of the 12 deaths occurred one to six weeks after randomization in patients with complete hemiplegia

10] Death from pneumonia at six weeks

11–12] Died suddenly of undetermined cause.

Treated (7 patients):

1] Sudden cardiac death at three months

2] Severe hemiplegia, died from shock, pyelonephritis, and gastrointestinal hemorrhage

3] Acute bilateral adrenal hemorrhage on eighth day

4] Complete hemiplegia, died on fifth day

5] Death from unexplained shock on eleventh day

6–7] Died of unknown cause at two months.

Embolism

Neurologic events in 1 control patient: Recovered well from initial right hemiparesis; on fifth day, had left hemiplegia and coma and died.

Treated (2 patients):

1] Admitted with left hemiplegia; sixteen hours after randomization, had right hemiplegia and coma and died–no evidence of hemorrhage

2] Right hemiparesis worsened temporarily on second day.

Deaths–Control (8 patients):

1] See patient 1 above

2] Death from cardiac failure at two months

3–8] Severe paralysis with death in one to ten days from pneumonia, infection, and so forth.

Treated (9 patients):

1] Died in sleep at fourteen months

2] Death from cardiac failure at two months

3] Sudden death at one and one-half months

4–9] Severe paralysis with death in one to four weeks of pneumonia, cardiac failure, and so forth.

An evaluation of anticoagulant therapy in the treatment of cerebrovascular disease

Report of the Veterans Administration Cooperative Study of Atherosclerosis, Neurology Section

ALTHOUGH ANTICOAGULATION THERAPY is now frequently advised in the management of cerebrovascular disease,[1–4] studies are needed in which the efficacy of this therapy is accurately evaluated by long-term, well-controlled investigations of large numbers of patients. Since the prognosis of cerebrovascular disease differs considerably with the various types of the disorder, a large reservoir of patients is required for the selection of suitable case material. For this reason, the most effective approach was thought to be a cooperative clinical investigation in which observations from several participating clinics were pooled.

The present study, conducted by neurologists from 9 Veterans Administration hospitals, is an attempt to determine the therapeutic value of anticoagulant drugs in cerebral ischemia and cerebral infarction. Simultaneously, a parallel cooperative study to evaluate the effects of long-term anticoagulant therapy of myocardial infarction was undertaken by a group of cardiologists working largely in the same hospitals and using the same research laboratory facilities.[5] These studies, together with an investigation of the dietary aspects of atherosclerosis, are part of a large-scale research program sponsored by the Veterans Administration Advisory Committee on Problems of Aging.

METHODS AND SELECTION OF CASE MATERIAL

To promote uniformity in diagnosis, treatment, and reporting, a detailed protocol was developed by the participating investigators in close cooperation with the statisticians of the National Academy of Sciences–National Research Council. Data from each hospital were submitted on standardized forms to the Follow-up Agency of the NAS-NRC for compilation and analysis. Uniform laboratory technics for prothrombin determinations were also established, and standard dilution curves using various control sera were checked periodically by a central laboratory (Bronx, N.Y.). Critical reagents, such as brain thromboplastin, were distributed to the participating hospitals from a single lot. Technical personnel from the central laboratory visited certain hospitals to assist in establishing a uniform procedure for prothrombin determination. In addition, a neuropathologist was designated to review the postmortem data and to examine the cerebral blood vessels and brain tissue of patients who died during the study. Serial samples of blood from each patient were sent to another laboratory (Durham, N. C.) for cholesterol determinations. Frequent meetings of the participating investigators were held to review case material, determine policies, and confer with the statisticians and with the clinical and laboratory consultants. These meetings were

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held periodically in conjunction with the cardiology group to compare findings from the two studies and to discuss mutual laboratory and follow-up problems.

Studies were made of 2 groups of patients with cerebrovascular disease. The first consisted of patients with transient cerebral ischemia, which was arbitrarily defined as "transient" if all or practically all of the neurologic manifestations cleared within twelve hours after onset. The second group consisted of patients with "completed" cerebral infarction in whom persistence of neurologic deficits for more than twelve hours indicated a destructive lesion of the central nervous system. Within these major diagnostic groups, the patients were subdivided into those with one known episode and those with more than one known episode. The latter were patients with at least 2 separate attacks of cerebral ischemia or infarction within the twelve months preceding admission to the study. Treatment included the use of anticoagulant drugs for approximately one-half of the patients within each of these 4 groups. In nearly every instance, the period of time between onset of the last cerebral episode and entry into the study was less than one month; in more than one-half of the cases, it was less than two weeks.

Rigid laboratory and clinical criteria for acceptance of cases were established in an attempt to exclude hidden cerebral hemorrhage, brain tumor, or embolism. In addition, patients with major medical complications, such as malignant hypertension, severe diabetes, neoplasm, or other metabolic disorders, were excluded. In an effort to minimize the hazards of anticoagulation therapy, patients with severe hepatic dysfunction, blood in the spinal fluid, hemorrhagic tendencies, or a history of ulcerative disease of the intestinal tract were not accepted into the study. Patients with extensive involvement of the central nervous system, coma, dementia, and personality disorders and those residing beyond a reasonable traveling distance from the hospital also were excluded.

Coumadin was the anticoagulant used in 7 of the participating hospitals; Dicumarol was the drug of choice in the other 2. Few patients were treated with heparin or intravenous anticoagulants. The dosage of coumarin agents was regulated by frequent prothrombin determinations during the minimum period of three weeks that patients were hospitalized and at intervals of one to three weeks after their discharge. The one-stage method[6] of determining the over-all prothrombin activity ("prothrombin time") was used.* Dosage was adjusted to maintain the prothrombin time at approximately 20% of the normal control time. During the first year of follow-up, exclusive of the first month, 1,234 prothrombin determinations were reported in percentage form during 2,177 patient-weeks of anticoagulant therapy. Of these determinations, 494 (40%) showed prothrombin times between 10 and 19% (Table 1). An additional 508 (41%) of the determinations showed prothrombin times between 20 and 29%.

TABLE 1
PROTHROMBIN DETERMINATIONS REPORTED IN PERCENTAGE OF CONTROL TIME DURING FIRST YEAR OF TREATMENT EXCLUSIVE OF FIRST MONTH

Prothrombin percentage	*Number of readings*	*Cumulative*	
		Number	*Percentage*
< 10	40	40	3.2
10-19	494	534	43.3
20-29	508	1,042	84.4
30-100	192	1,234	100.0

There were 2,177 weeks during which anticoagulants were given to patients in the treated group.

Patients treated with anticoagulants returned on an average of every two weeks for prothrombin determinations. This group, along with the control subjects, were interviewed and examined not less than once a month for evidence of recurrent vascular disease. Both groups of patients received whatever other medical therapy seemed necessary, such as specific diets, physical therapy, or antihypertensive medications.

To minimize bias in the designation of therapy, patients were assigned to the treatment and control regimens at random through the use of consecutively numbered sealed en-

*Specific prothrombin time, proconvertin-convertin determinations, and, more recently, Stewart factor determinations were also made in an attempt to explain unexpected episodes of bleeding or thromboses. The results of these studies will be reported later.

TABLE 2
NUMBER OF PATIENTS SCREENED, ACCEPTED, AND FOLLOWED

	Screened	*Randomized*	*Not followed*	*In study*
Ischemia				
Single	63	15	2	13
Multiple	116	33	9	24
Infarction				
Single	671	115	21	94
Multiple	198	26	2	24
Unknown	361			
Total	1,409	189	34	155

velopes. However, because the patients receiving anticoagulants necessarily were seen more frequently and because each investigator necessarily was aware of the treatment allotted to a given patient, it is possible that the interpretation of recurrent symptoms and neurologic signs was not free of bias. For this reason, evaluation of the therapeutic effect was not based upon the degree or speed of recovery from the initial vascular accident but was based upon either survival of the patient or the occurrence of new cerebral infarcts and well-defined episodes of cerebral ischemia. It was believed that these gross indexes of treatment failure were less likely to be influenced by investigative bias. In addition, the chairman of the study group reviewed the clinical records of all patients who died and of all patients who experienced recurrent vascular episodes in an effort to ensure consistency of evaluation.

RESULTS

Analysis of cases accepted and lost from the study. Of 1,409 patients screened from January 1958 through December 1959, 189 satisfied the protocol requirements (Table 2); 34 patients were later taken out of the study because of a change in diagnosis or because follow-up observations could not be obtained for more than one month. The remaining 155 patients represent the case material in this study and were equally divided between treatment and control groups. The control group was observed for an average period of 12.8 months as compared to 9.3 months for the patients receiving anticoagulants. The groups were comparable with respect to age and site of involvement of cerebral vessels, but the control group had a slightly higher reported incidence of cardiac abnormalities: 48% as compared to 33% in the treated patients. All patients were male; 15 were nonwhite.

Of the 155 patients accepted into the study, 14 defaulted or were lost from the study because they were unable to cooperate in taking their medication or were unable to return at frequent intervals for prothrombin regulation (Table 3). For 22 additional patients, the assigned treatment was discontinued permanently for such reasons as major surgery, unrelated illnesses, cerebral or myocardial infarctions, and bleeding. In 4 instances, the individual investigator elected to stop treat-

TABLE 3
PATIENTS DYING, LOST TO FOLLOW-UP, OR WITH CHANGES IN TREATMENT

	Patients accepted for study	*Unable to return or cooperate*	*Treatment changed*	*Deaths during active follow-up*	*Patients currently in study*
Ischemia					
Treated	22	2	6	1	13
Control	15	1	1	0	13
Infarction					
Treated	56	6	11	12	27
Control	62	5	4	7	46
Total					
Treated	78	8	17	13	40
Control	77	6	5	7	59

TABLE 4
THROMBOTIC EPISODES AFTER RANDOMIZATION

	Number of patients	Cerebral episodes		Other vascular episodes		Total number of episodes
		Ischemia	Infarction	Coronary	Pulmonary-peripheral	
Ischemia						
Treated	22	1	1	1	0	3
Control	15	8*	0	0	0	8
Infarction						
Treated	56	1	3	1	1	6
Control	62	3	4	2	4	13
Total						
Treated	78	2	4†	2	1	9
Control	77	11	4	2	4	21

*2 of these patients had either myocardial infarction or peripheral vascular disease.
†An additional 3 patients had cerebral infarction within three weeks after anticoagulation was discontinued.

ment at the end of one year. These losses, along with 20 deaths, reduced the number in the study as of February 29, 1960, to 99 cases, of whom 59 are in the control group. This rate of attrition has also been observed by others in studies of anticoagulants in an aged population.[7] Anticoagulation was temporarily discontinued in 12 patients because of minor bleeding and in 9 patients because of minor illnesses.

Effect of treatment upon recurrent vascular episodes. During follow-up, emphasis was placed chiefly upon the recurrence of cerebral infarction and the development of definite new cerebral ischemic attacks. Attention was also given to vascular episodes elsewhere in the body, such as coronary thrombosis, occlusion of peripheral arteries, or pulmonary embolism. The numbers of patients with such recurrent vascular episodes are shown in Table 4.

After entry into the study, 13 patients had well defined episodes of transient cerebral ischemia; 2 of them were in the treatment group, and 11 were control subjects. Of the 2 treated patients, 1 had ischemia within two weeks after anticoagulation was started and the other had 2 to 5 attacks eighteen months later. The 11 patients in the control group had an average of 2 to 5 ischemic attacks during the first three months after randomization, but a few of them had as many as 10 to 20 recurrent episodes during this period.

During the period of follow-up observation, 8 patients had new cerebral infarcts; 4 were in the treated group, and 4 (1 of whom died) were control subjects. The recurrence rate of cerebral infarction in the control subjects during the first year of observation was estimated, by life table procedures, to be 4% as compared to 2% in the treated group. The 4 treated patients had prothrombin levels in the desired range (16 to 23%) during the week before their infarctions. It should be noted, however, that 3 additional patients had cerebral infarction approximately three weeks after their anticoagulants were discontinued because of surgery or bleeding episodes; 2 of these patients had either a serious illness or an operation, which may have been a factor in the development of their recurrent infarction.

Clinical and electrocardiographic evidence of myocardial infarction appeared in 3 patients in the control group, 1 of whom also had cerebral ischemia, and in 2 patients in the treatment group, both of whom died; 3 other patients receiving anticoagulants died abruptly after onset of chest pain or sudden congestive failure and may also have had myocardial infarction. Considering all the major vascular occlusive episodes, that is, exluding those with cerebral ischemic attacks only, 12 patients were in the control group and 7 in the treated group ($p > .05$).

Effect of treatment on mortality. The mortality rate among patients treated with anticoagulants was higher than in the control

TABLE 5
NUMBER OF DEATHS AMONG TREATED AND CONTROL CASES

	Number in study	Deaths Number	Deaths Percentage
Single ischemia			
Treated	10	1 (1)*	20.0
Control	3	0	0.0
Multiple ischemia			
Treated	12	0	0.0
Control	12	0	0.0
Single infarction			
Treated	46	8 (2)	21.7
Control	48	4 (3)	14.6
Multiple infarction			
Treated	10	4	40.0
Control	14	3	21.4
Total			
Treated	78	13 (3)	20.5
Control	77	7 (3)	13.0

*Deaths occuring after termination of follow-up are shown in parentheses.

group (Table 5). Disregarding the 6 deaths among patients lost from follow-up, the mortality rate in the control subjects during the first year of observation, estimated by life table procedures, was 6% as compared to 19% in the group receiving anticoagulants.

Only 3 patients (all of whom received anticoagulants) died within one month after randomization; 4 others (2 each in the treatment and the control group) died in the second and third months. Almost all of the remaining patients died late in the period of observation, the majority of the treated patients dying in six to eight months, whereas most of the control subjects died in ten to fifteen months. These differences in the time of death account in part for the higher life table mortality rate observed in the treated patients.

Causes of death are shown in Table 6. Autopsy examinations were obtained for 9 of the 13 treated patients and for each of the 7 control subjects. One of the patients who died of an intracranial hemorrhage had hypertensive disease, with blood pressure readings as high as 230/140 mm. Hg. His last prothrombin determination was 17%. Another patient with massive intracranial bleeding had a prothrombin time of 34 sec. (less than 10%) the day before onset of the hemorrhage. The third patient had clinical evidence of a cerebral hemorrhage two weeks after his last prothrombin determination was found to be 50%. The fourth hemorrhagic death was caused by rupture of a syphilitic aneurysm of the aorta, the last prothrombin time two days previously being 23%. The 1 patient in the control group who died of a cerebral hemorrhage was normotensive and was found at autopsy to have massive pontine bleeding.

While myocardial infarction was found on postmortem examination to be the cause of death in 2 of the treated patients, in 3 others, mentioned above, myocardial infarction was probably the terminal episode. The exact cause of death in most of the 6 patients who died after termination of follow-up was undetermined since knowledge of their deaths was obtained largely from administrative records of the Veterans Administration.

Hemorrhagic complications. In addition to the 4 massive hemorrhages which resulted in death, there were 6 other major but nonfatal hemorrhagic complications in the treated group (Table 7); 3 of these patients had intracranial bleeding, with prothrombin determinations of 31, 13.5, and less than 10% (41 sec.), respectively, a few days to a week before onset of their bleeding episodes. Each of these 3 patients with cerebral bleeding had moderate blood pressure elevations ranging from 150/70 to 170/100. Severe gastrointestinal hemorrhages from peptic ulcer or colostomy developed in 3 others, with prothrombin times

TABLE 6
CAUSES OF DEATH DURING ACTIVE FOLLOW-UP

	Treatment	Control	Total
Massive hemorrhage	4	1	5
Cerebral infarction	2*	1	3
Cardiac disease	5	1	6
Pulmonary thromboembolism	0	2	2
Other or unknown	2	2	4
Total	13	7	20

*Both patients died of their initial cerebral infarction within four weeks after randomization.

ranging from less than 10 to 39%. In the control group, 3 patients had major hemorrhages, 1 of which was fatal and consisted of the massive pontine hematoma mentioned above. Minor hemorrhages in the urinary tract, skin, and bowel were noted in 21 of the patients treated with anticoagulants and in only 2 control subjects.

TABLE 7
HEMORRHAGIC COMPLICATIONS

	Number of patients	
	Treatment	*Control*
Major		
Cerebral	6 (3)*	1 (1)
Gastrointestinal	3	2
Rupture of aneurysm	1 (1)	0
Minor	21	2
Total	31 (4)	3 (1)

*The number of patients who died as a result of bleeding is shown in parentheses.

DISCUSSION

Previous reports on the use of anticoagulants in cerebrovascular disease have emphasized the value of these agents in preventing recurrent ischemic attacks and in aborting an impending cerebral infarction.[2] A few studies advise anticoagulation for the treatment of "complete" cerebral infarction, especially in patients with basilar artery occlusion or with thromboembolism involving other organs of the body.[1,3] The present investigation of long-term anticoagulation demonstrates neither a significant reduction in the recurrence of cerebral infarction nor a decrease in the mortality rate associated with this illness. Although there is some evidence in this study to suggest that recurrent episodes of cerebral ischemia are prevented by this form of treatment, the incidence of cerebral infarction in these patients was so small that the role of anticoagulation in preventing this vascular lesion could not be determined. The same consideration applies to patients with single or multiple "complete" infarcts. Only 7% of our control patients with cerebral infarction had another stroke during the period of observation, an incidence comparable to that of 9% per year noted in other studies on the natural course of this disorder.[8]

Not only was the incidence of recurrent cerebral infarction apparently unaltered by anticoagulation, but the treated patients had a higher mortality rate than the controls. This increase in deaths was due partly to the occurrence of cerebral hemorrhage, a complication which has been observed in other studies and which is regarded as a major risk in anticoagulant therapy of cerebrovascular disease.[4] Although differentiation of cerebral thrombosis from cerebral hemorrhage may at times be difficult, such mistakes in diagnosis, to our knowledge, were not made in any of the patients in this study. However, 1 patient was found on postmortem examination to have a large aneurysm of the basilar artery without evidence of bleeding. Anticoagulation had been discontinued several months previously because of hematuria and mild subarachnoid bleeding. Such misdiagnoses are certain to occur despite the most careful clinical examination.

Patients with cerebrovascular disease seem to have many more contraindications to long-term anticoagulation than those with other vascular disorders. The neurologic lesions in these patients may produce physical disabilities preventing frequent return visits for prothrombin regulation, or disturbances in speech or mental function may be present and impair their understanding of instructions for anticoagulant administration. Further, these patients are often in the older age groups and, as a consequence, are likely to have other surgical or medical illnesses requiring cessation of anticoagulation therapy. All of these factors contribute to the high exclusion rate and to the number of patients defaulting or lost from studies such as this. It would appear, therefore, that the 11% of patients found acceptable for long-term anticoagulation in this study applies as well to other groups of patients with this illness. It is inescapably apparent that other methods of treating cerebrovascular disease are needed.

This study was not designed to assess the effects of rapid anticoagulation, which is held by some investigators to retard the progression of actively advancing cerebrovascular occlusion ("thrombosis in evolution").[2,9] However, once the advancing process has ceased, the effects

of long-term anticoagulation observed in the present study presumably would apply to these patients as well. The small number of patients with cerebral ischemia who had cerebral infarction was indeed surprising, since previous observations indicated that such patients frequently have permanent or severe neurologic deficits. Our arbitrary definition for cerebral ischemia permitted the acceptance of patients with neurologic manifestations for as long as twelve hours after onset. For this reason, patients with small cerebral infarcts may have been included in the category of cerebral ischemia. In addition, approximately one-third of these subjects had only a single ischemic episode before randomization, and such cases may have a prognosis quite different from those of multiple transient ischemic attacks. Nevertheless, it appears that the commonly accepted view that transient cerebral ischemia is usually followed by cerebral infarction may need to be revised.

In general, it appears that anticoagulant therapy may be indicated in patients with transient cerebral ischemia in an attempt to reduce the number of subsequent ischemic attacks. Although a longer period of follow-up observations on these patients may reveal that cerebral infarction is prevented or postponed by this form of treatment, the present study does not permit any such conclusion. On the other hand, anticoagulant therapy appears to have little or no value in patients with "completed" cerebral infarction, that is, those without evidence of recurrent ischemia or advancing neurologic deficits. In such cases, the risks of serious hemorrhagic complications from long-term anticoagulant therapy do not seem justified.

SUMMARY

A cooperative clinical investigation was undertaken in 9 Veterans Administration hospitals to determine the effects of long-term anticoagulant therapy in cerebrovascular disease. Only 11% of patients with this dease were found to be acceptable for this treatment.

The 155 patients studied had manifestations of either cerebral ischemia or cerebral infarction and were divided equally on a random basis between treatment and control groups. These groups were observed for an average period of about nine and twelve months, respectively, after entering the study.

Although anticoagulation appeared to decrease the number of attacks of cerebral ischemia, there was no reduction in the incidence of new or recurrent strokes. A higher mortality rate was found in the treated patients, due in part to the hemorrhagic complications.

On the basis of the observations made thus far, long-term anticoagulation does not appear to be a practical or effective method of treatment for the majority of patients with cerebrovascular disease caused by atherosclerosis.

Paper presented by Robert N. Baker, M.D.

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Discussion on anticoagulant therapy of cerebrovascular disease

John Marshall, M.D.

I WOULD FIRST LIKE TO THANK the organizers for their kindness in inviting me to open the discussion on this section of the conference and to express my appreciation of the papers given by Dr. Miller Fisher and Dr. Baker.

In the Institute of Neurology in London, we have, over the past three years, been conducting experiments along similar lines. Some of these studies have been complementary to yours, and I propose therefore to lead discussion on these two papers in light of my own experience in this field.

Nearly all of us who are interested in the treatment of cerebrovascular disease are in agreement on one general point—the absolute necessity for controlled trials because of the variable pattern and uncertain natural history of the condition. Implicit in this requirement is the need for sound statistical design and analysis. Moreover, the possibility of hazard from anticoagulant therapy demands an experimental design which will be as economical as possible in the use of case material.

In our studies, we have tackled some, but not all, of the problems raised by the two speakers, and many of our conclusions are in agreement with theirs. Unlike them, we have chosen to consider the acute and long-term problems quite separately because it seems to me that the role of anticoagulants and their hazard in the acute disease may be quite different from their purely preventative role in the care of patients who, on the basis of a previous stroke, are presumed to have cerebral atherosclerosis and to be liable to further episodes of cerebral ischemia or infarction.

Let us deal with the acute cases first. Dr. Miller Fisher has shown that his patients with fully developed stroke, most of whom I presume to have been first treated in the acute phase and to have been carried on a long-term basis, have not so far benefited from anticoagulant therapy. At this point, there is a question I would like to ask Dr. Miller Fisher. How many of the deaths and, particularly, how many of the deaths *due to* anticogulant therapy in Group III occurred during the first three or four weeks of treatment? My own experience has shown that anticoagulation during the acute stage in cases of fully developed stroke is not beneficial. This conclusion is based on an experiment which I would like to describe.

Studies were made on 51 patients below the age of 70 who had diagnoses of nonembolic, nonhemorrhagic infarction on the basis of clinical examination, lumbar puncture, and cerebral angiography; they were randomized between treatment and control groups. On the basis of the anatomic site of lesion and age distribution, the composition of these groups was almost identical. Patients were not eligible unless treatment could be started within seventy-two hours, and both groups were managed in the same way in all respects except that members of the treatment group were given phenindione, augmented by intravenous heparin in the first twenty-four hours, for a period of three weeks. The prothrombin time was kept at 2½ to 3 times the control time. In the knowledge that the treatment might prove harmful, it was felt essential that results should be subject to statistical analysis as they came through, so that a definitive answer would be immediately apparent. Classic tests of significance are of course inappropriate to this type of running analysis, and I therefore adopted a sequential design. It has been shown that, according to our criteria of selection and management, anticoagulants confer no benefit in the acute stroke.

It should be stressed that no account was taken of the rapidity or extent of progression of the cerebral infarct, and my results do not imply that the limited subgroup of stroke-in-evolution may not be benefited as Dr. Miller Fisher's figures suggest. Indeed, we are at present conducting a trial in respect to this particular subgroup of ingravescent strokes.

Now let us turn to the question of long-term anticoagulants for the prevention of strokes in patients known to suffer from cerebral atheroma on the basis of previous infarcts. I started a trial in October 1957 which included patients under the age of 70 who were again randomized into treatment or control groups, the only difference being that the treated group received phenindione in order to keep their prothrombin times at 2 to 2½ times the control time. These patients were admitted to the trial at any time after a cerebrovascular episode, provided at least fourteen days had elapsed. Again, this experiment was broad in design, and patients were included regardless of the site of the vascular lesion. By June 1959, 142 patients had been included in the trial, and an analysis at this stage showed the following results. There were 5 nonfatal recurrences of cerebrovascular accidents in 4 patients in the treatment group and 4 similar recurrences in 3 patients in the control group, clearly not a significant difference. On the other hand, in the treated group, there were 4 fatal cerebrovascular accidents, all cerebral hemorrhages, and, in the control group, there were none. Also, in the treated group, a patient died of hemopericardium, and it was thought that this must be attributed to therapy. We thus have 5 deaths in the treated group and none in the control group. We see that the odds of this difference occurring by chance are about 17 to 1.

In light of these results, it was apparent that anticoagulants are not to be recommended for the broad spectrum of cerebrovascular patients included in this experiment and that, as in the acute trial, we must refine our experiment and consider more limited subgroups. Although there were no clear indications in the results to date, there was a trend which suggested that it was the hypertensive patients who on the whole were responsible for the adverse result. This observation is supported by Dr. Miller Fisher's data as well as by those of other workers. I therefore decided to withdraw from the trial all those patients who were hypertensive but in other respects to continue as before. Since then, we have encountered fewer deaths from cerebral hemorrhage and no fatal complications of treatment, but it is as yet too early to draw any definite inference from our further data.

In conclusion, I would say that my impression, based on my own experience and that of others, is that anticoagulants may be of value in two situations—the stroke-in-evolution and the recurrent transient ischemic attacks. But I do not think that we have as yet adequate evidence to prove this. I think that it is imperative that such evidence be obtained before we allow this treatment, which is not without hazard, expense, and inconvenience, to become more widely used than it is already.

Discussion on anticoagulant therapy

Sigmund N. Groch, M.D.

THE PROBLEMS of conducting a long-term clinical study are many and can never be adequately detailed in a paper. One has to live with the problems that continuously arise to appreciate fully the difficulties involved. Both Dr. Fisher and Dr. Baker deserve our unqualified gratitude for their devotion and enthusiasm, without which these studies undoubtedly would have failed.

In considering the question of anticoagulant therapy for strokes, it is soon apparent that one must deal with the subject in the three separate phases found in the evolutionary pattern of a stroke. The recent reports of Millikan and associates and of Fisher indicated that anticoagulant therapy could be used most effectively in patients in the first phase, the period of intermittent ischemic attacks. The results reported by the Mayo Clinic group were so impressive that one would expect to have no difficulty in verifying them by means of a randomized study. At the time of the writing of this paper, Dr. Muench, the consultant in biostatistics for the N. I. H. Cooperative Study, would only say that these figures "possibly" were significant.

Undoubtedly, a larger series would be more helpful. Nevertheless, it would seem that the earlier reports of anticoagulant therapy for intermittent cerebral ischemia have been supported by the N. I. H. results.

Our group sees very few patients at the time they are experiencing transient ischemic episodes, although the episodes are well detailed in the histories of at least 25% of the patients in the study. We are therefore gratified that the Cooperative Study as a whole has been more successful than we have been. What remains to be answered is how many of the patients in the control group will experience serious neurologic difficulty and how long after the onset of the cerebral ischemic episodes will this occur.

In recent reports, particularly those of Fisher and of Carter, the patient in phase 2, the stage of an evolving stroke, was said to be benefited by the use of anticoagulant therapy. While Dr. Muench again would use the words "possibly significant," this concept receives support from Dr. Fisher's report.

Before dealing with the third phase in the evolution of a stroke, I should like to examine certain problems that have been presented by Dr. Fisher. Several deaths in the N. I. H. Group treated with anticoagulants were due to hemorrhage. In a very large proportion of these patients, the hemorrhagic complication occurred either in a patient with severe hypertension or in a patient in whom the prothrombin time was prolonged excessively at the time of death. This underscores 2 of the dicta that have guided our study: [1] avoid the use of anticoagulant therapy in patients with group III or IV hypertensive retinopathy and in patients with group II hypertensive changes in the fundus who have diastolic blood pressures of 120 or greater and [2] do not carry the

Cerebral Vascular Disease Study
Bellevue Hospital -- July 20, 1956 to January 31, 1960

COMPOSITION OF SERIES

Total number	558
Male	328
Female	230
Suitable for randomization	181
Randomized treats	92
Randomized controls	89
Never randomized	377
Obligatory treats	57
Contraindicated	143
Too ill or administrative complications	177

Fig. 1. Composition of series

COMPOSITION OF SERIES

Total patients	558
Clinical diagnoses:	
Cerebral embolus	29
Cerebral hemorrhage	71
Primary intracerebral	40
Primary subarachnoid	31
Cerebral thrombosis	393
Basilar vertebral tree	56
Carotid and branches	337
Tumor simulating stroke	9
Subdural hematoma simulating stroke	8
Indefinite diagnosis	48

Fig. 2. Clinical diagnoses

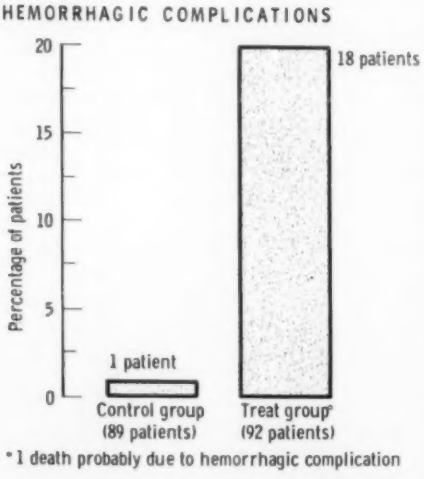

Fig. 3. Incidence of hemorrhagic complications in randomized series

prothrombin time at a level greater than 2½ times the control. Admittedly, this is not always possible, and excessive levels are an inevitable consequence in some of the patients included in a large series treated with anticoagulant drugs for an extended period of time.

It is the opinion of our group that the method of prothrombin time determination used in our laboratory may be helpful in deciding when a patient's prothrombin time may be heading in the undesired direction. A reading of greater than three minutes in the 12½% dilution of the patient's plasma, when performed by the Link-Shapiro modification of the Quick test, using a thromboplastin that is not derived from brain, is a warning to lower dosage of the anticoagulant, even though the undiluted specimen still may be within therapeutic range. Moreover, the dilute determination correlates well with appreciable depression of the Stewart-Prower factor (Factor X), prothrombin concentration, and Factor VII (Stabile factor, SPCA) before the undilute time has reached excessive levels. An abnormality of Factor X or prothrombin concentration well may be the cause of bleeding when a patient's prothrombin time is "within therapeutic range."

It has been suggested that a review of the results of the Bellevue Study, which is now approaching the end of the fourth year, may prove of interest to you and also aid in answering certain important questions:

1] What number of any large group of patients with stroke are suitable candidates for anticoagulant therapy?

2] What does such therapy offer a patient with a complete stroke?

3] What are the risks of long-term therapy, particularly in a group similar to the one seen at a municipal hospital such as Bellevue?

The first illustration describes the composition of the series through January 30, 1960 (Fig. 1). The important point to be emphasized is that only one-third of the entire group were considered suitable for randomization. In the Veterans Administration Study, an even smaller proportion of patients screened were found suitable for randomization. A small number were thought to require therapy on an obligatory basis because they had an underlying pathologic process for which we feel anticoagulants are considered mandatory, particularly patients with myocardial infarction or patients for whom a clinical diagnosis of cerebral embolus has been made. A majority of the group who were not randomized were thought unsuitable for such therapy for the following reasons:

1] The circumstances of the onset of the stroke were unknown, and no history was obtained.

2] Recent history of active duodenal ulcer was elicited.

3] A hemorrhagic diathesis or blood dyscrasia was found.

4] Severe hypertension was present.

5] The patient remained in a continuous state of coma for twenty-four hours or longer.

6] The patient had a critical complicating illness or appeared terminal.

7] Permission was not granted for a cerebrospinal fluid examination.

8] The cerebrospinal fluid was either grossly bloody or xanthochromic.

9] Severe liver or renal disease was present.

In Figure 2, the clinical diagnoses are detailed. These are not final diagnoses for many of the patients, and there will undoubtedly be some changes when a final review of the complete files is made. Simulation of the clinical picture of nonhemorrhagic infarction by tumor and subdural hematoma has been well described in the past. Included here are those patients in whom the diagnosis of a mass lesion was made by angiography, surgical exploration, or postmortem examination. Angiography has proved to be a most helpful diagnostic aid to us, although the morbidity at times has been excessive.

Figure 3 details the hemorrhagic complications encountered in the randomized patients. The patient in the control group was one who was randomized as a control and, three weeks after discharge from the hospital, reentered with a fatal cerebral hemorrhage. There has been one death to date attributable to anticoagulant therapy. This individual died suddenly during the second week of anticoagulant therapy, and, at autopsy, approximately 500 cc. of blood was present in the retroperitoneal space. There were 2 hemorrhagic complications involving the central nervous system, 1 of which was a worsening of the clinical status and the other a subarachnoid hemorrhage occurring in the tenth month of anticoagulant therapy, at a time when the prothrombin determination was at the outer limits of therapeutic range. Bilateral carotid angiograms in this patient were normal. Both of these patients

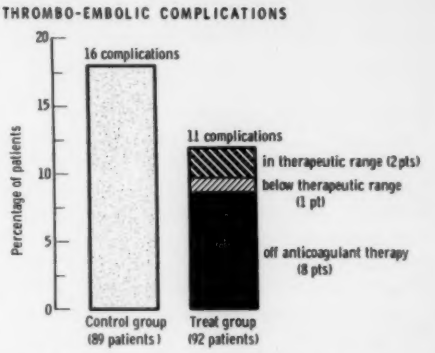

Fig. 4. Thromboembolic complications in randomized series

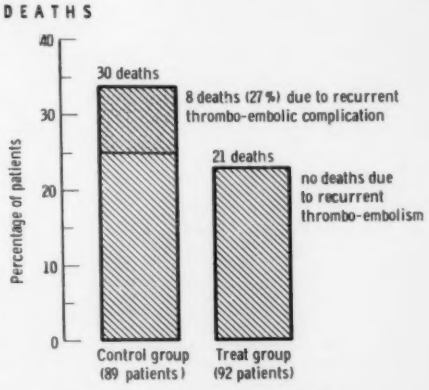

Fig. 5. Mortality rate in randomized series

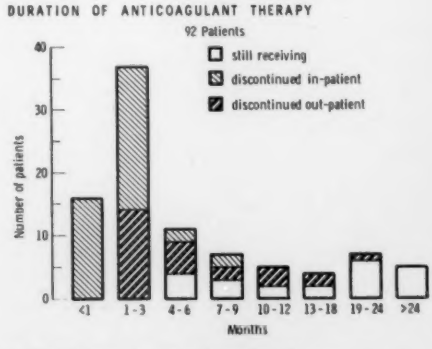

Fig. 6. Duration of anticoagulant therapy

survived these complications. In some of the patients, hemorrhage was the first and only sign of underlying disease of the gastrointestinal and genitourinary systems, and, in a few, no cause for bleeding could be found.

In Figure 4, the recurrent thromboembolic episodes are depicted. Of the 16 in the control group, 9 complications were strokes and the remainder consisted of myocardial infarction (2), pulmonary embolus (3), and femoral vein thrombophlebitis (2). Many of these complications occurred after the first year of observation. In the treated group of patients, 9 of the episodes affected the central nervous system. However, it is important to emphasize that 8 patients in whom anticoagulant therapy had been discontinued before the recurrent episode are included in the column depicting the "anticoagulant treatment group."

Figure 5 illustrates mortality for the randomized series. The important feature to be stressed is the difference in mortality due to recurrent thromboembolism in the 2 groups. While there were no deaths due to recurrent thromboembolism in the treated group, 8 of 30 deaths in the control group resulted from recurrent thromboembolism.

In Figure 6, the duration of anticoagulant therapy for the 92 randomized patients is illustrated. We have found it difficult to continue anticoagulants on an outpatient basis in many of the patients we have encountered.

This is undoubtedly a major problem in any long-term clinical study that deals with a patient population similar to that seen in Bellevue Hospital.

A word of caution must be interjected at this time. The results of our study as presented today are still only preliminary and are not to be considered as statistically valid. While the trends depicted have been consistent with each yearly review, we know that these patients must be followed for a longer period of time.

In summary then, it would seem that anticoagulant therapy is suitable for only a small number of any large group of patients with the clinical picture of stroke. It certainly should be used with great caution, if at all, in patients with appreciable hypertension. Great care is necessary to keep the prothrombin time from reaching excessive levels. The use of the 12½% dilution of the patient's plasma, with a nonbrain thromboplastic substance, may be helpful.

The N. I. H. Study supports the concept that advocates the use of anticoagulant therapy for transient ischemic attacks and for a stroke in evolution. The role of such treatment in the completed stroke is not clarified at this time and certainly should not be considered as routine therapy. Moreover, the risk of hemorrhagic complications is ever-present.

Surgical treatment of patients with cerebral arterial insufficiency associated with extracranial arterial occlusive lesions

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THE SEGMENTAL NATURE of the atherosclerotic occlusive process causing arterial insufficiency, regardless of location, has been well established during the past two decades. This fortunate pathologic feature of the disease process has permitted the development and application of surgical technics designed to restore normal blood flow in the region of obstruction by approaching the occluded arterial segment directly. This approach was first employed in the treatment of lesions of the aorta and iliac, femoral, and popliteal arteries causing arterial insufficiency of the lower extremities. These lesions, being associated with intermittent claudication, rest pain, painful ischemic ulceration, and gangrene, have challenged physicians and surgeons alike for centuries, and the effectiveness of reconstructive operation over the past eight years in these cases is now well established. In fact, this method of therapy is recognized as the only form of treatment which assures immediate relief of pain and reversal of advanced ischemic changes in the tissues. The lesions causing cerebral arterial insufficiency have been demonstrated to be similar and are frequently accessibly located in the extracranial segments of cerebral circulation. For this reason and because of the poor results generally associated with therapy not directed toward the occlusive process and designed to restore a normal distal pulsatile blood flow, it was only natural to consider arterial reconstructive operation, which had proved so successful in the treatment of occlusive lesions occurring elsewhere. This report is concerned with our experience with this form of therapy since August 1953 in 622 patients; symptoms had developed in 10 during anticoagulant therapy given for heart disease, and one-third had been referred because they either had not improved or had become worse while receiving anticoagulant therapy.

Early in our experience, it became obvious that operable extracranial lesions frequently were not apparent on clinical grounds, although murmurs, pulse changes, and certain symptoms were highly suggestive of this form of the disease. For this reason, arteriography was employed as a routine method of study in all patients with symptoms suggesting cerebral arterial insufficiency, regardless of extent. Moreover, because of the frequency of multiple lesions, bilateral carotid and bilateral transsubclavian vertebral arteriograms were performed in most cases and thoracic aortograms were performed in many. These procedures were performed during local anesthesia and were proved to be safe despite the frequency of multiple occlusion and the poor condition of some patients. Death occurred after arteriography in only 2 cases, as a result of cardiac arrest in one and of basilar artery insufficiency in the other. The clinical manifestations of cerebral arterial insufficiency progressed in 2 patients immediately after arteriography. However, both patients were com-

TABLE 1

OCCLUSIVE DISEASE OF INNOMINATE, CAROTID, SUBCLAVIAN, AND VERTEBRAL ARTERIES IN 208 PATIENTS

Location	Number of lesions	Lesions explored		Circulation restored	
		Number	Per cent	Number	Per cent
External carotid	9	9	100	8	89
Internal carotid	256	211	82	185	88
Common carotid	16	16	100	16	100
Innominate	16	15	94	15	100
Subclavian	29	27	93	27	100
Vertebral	55	32	58	29	91
Total	381	310	81	280	90

pletely relieved by an immediate operation.

Cerebral arteriography, as previously described, was employed in the study of 622 consecutive patients with clinical manifestations suggesting cerebral arterial insufficiency. Extracranial lesions located in the internal carotid arteries, vertebral arteries, and great vessels arising from the aortic arch were demonstrated in 226 patients, or 40% (Tables 1 through 3). Operation was employed in the treatment of 208 patients in whom the lesions were considered sufficiently advanced to cause reduction in blood flow (Table 4). There were 381 extracranial arterial occlusive lesions in this group of patients, indicating the frequency of multiple lesions and emphasizing the limitation of collateral blood flow (Tables 1 through 4). Of the 381 lesions, 310 were explored surgically. The remaining lesions either were inoperable because of their extensive nature or were considered to be associated with obstruction insufficient to cause reduction in blood flow and therefore did not require operation at the time of study. Of the 310 lesions explored, 297 were localized and suited to reconstructive operation. The remaining 13 lesions, located in the internal carotid and vertebral arteries of patients with symptoms of long duration, proved to be inoperable because of the extent of the occlusive process.

The type of operation employed varied with the location and extent of the occlusive process. Discrete, well-localized lesions in the internal carotid and vertebral arteries usually were treated by endarterectomy performed through a longitudinal incision closed by insertion of a patch graft to prevent lumen constriction. The more extensive lesions, usually located at

TABLE 2

OCCLUSIVE DISEASE OF INNOMINATE, CAROTID, SUBCLAVIAN, AND VERTEBRAL ARTERIES IN 208 PATIENTS

Type of occlusion	Number of lesions	Lesions explored		Circulation restored	
		Number	Per cent	Number	Per cent
Proximal					
Complete	29	28	97	28	100
Partial	32	30	94	30	100
Distal					
Complete	64	29	45	10	34
Partial	256	223	87	212	95
Total	381	310	81	280	90

or near the origins of the great vessels arising from the aortic arch, were treated by application of the bypass graft principle.

The anatomic or vascular results of operation varied with the location and extent of the occlusive process (Tables 1 through 4). Circulation was successfully restored in the region of operation in all patients with proximal occlusion of the larger vessels arising from the aortic arch, regardless of extent of occlusion, and in 95% of patients with partial occlusion of the internal carotid and vertebral arteries. Of the 29 patients with complete occlusion of the latter vessels, blood flow was restored in 10 patients, or 34% (Table 2).

All patients with possible operable lesions, regardless of clinical manifestations, were submitted to operation, and the functional results

TABLE 3

OCCLUSIVE DISEASE OF INNOMINATE, CAROTID, SUBCLAVIAN, AND VERTEBRAL ARTERIES IN 208 PATIENTS

Type of occlusion	*Number of arteries involved*				*Total*
	1	*2*	*3*	*4 or more*	
Complete	19	7	1	1	28
Partial	64	52	10	4	130
Combined	0	33	10	7	50
Total	83	92	21	12	208

TABLE 4

OCCLUSIVE DISEASE OF INNOMINATE, CAROTID, SUBCLAVIAN, AND VERTEBRAL ARTERIES: SURGICAL TREATMENT IN 208 PATIENTS

Type of operation	*Number of cases*	*Circulation restored Number of cases*	*Per cent*
Thromboendarterectomy	235	218	93
Graft bypass	62	62	100
Exploration only*	13	0	0
Total	310	280	90

*Complete occlusion of long duration

TABLE 5

IMMEDIATE RESULTS IN PATIENTS WITH CAROTID ARTERY INSUFFICIENCY

Neurologic symptoms	*Deaths*	*No change*	*Improved*	*Asymptomatic*	*Total*
Prophylactic*	0	0	0	17	17
Transient attacks	2	1	0	46	49
Persistent progressive	1	1	8	2	12
Completed stroke					
Homolateral artery†	1	11	9	0	21
Contralateral artery‡	4	5	26	11	46
Exploration only	4	10	1	0	15
Total	12	28	44	76	160

*No symptoms
†Artery located on same side of body as symptom
‡Artery located on side of body opposite symptom

TABLE 6

LATE RESULTS IN PATIENTS WITH CAROTID ARTERY INSUFFICIENCY

Neurologic symptoms	*Deaths*	*No change*	*Improved*	*Asymptomatic*	*Total*
Prophylactic*	1	0	0	15	16
Transient attacks	1	1	1	31	34
Persistent progressive	0	1	5	4	10
Completed stroke					
Homolateral artery†	1	6	7	2	16
Contralateral artery‡	3	3	15	17	38
Exploration only	4	0	2	0	6
Total	10	11	30	69	120

*No symptoms
†Artery located on same side of body as symptom
‡Artery located on side of body opposite symptom

varied with duration of follow-up, location of lesion, and severity of symptoms (Tables 5 through 8). For purposes of evaluating functional results, the patients were divided into 2 groups according to symptoms, regardless of whether the patient survived operation or circulation was restored; 1 group consisted of all patients with symptoms of basilar insufficiency (Tables 7 and 8) and the other group, of patients with symptoms of carotid insufficiency (Tables 5 and 6). Each group was subdivided according to type and severity of symptoms. For example, patients who had completely recovered from symptoms at the time of operation were recorded as having transient attacks. Patients in whom symptoms were persistent and progressive in nature were labeled as persistent progressive. All patients with a persistent, stabilized neurologic deficit were considered to have a completed stroke. The deficits in these cases ranged from mild monoparesis to complete hemiplegia. These groups were subdivided further according to type of operation and location of the lesion in relationship to the neurologic deficit. Immediate results (during the period of hospitalization) are presented for all 208 patients having operations before May 1, 1960, and late results are presented for 152 patients having operations before January 1, 1960 (follow-up ranging from four to seventy-six months).

Prophylactic internal carotid artery endarterectomy was performed in 17 patients admitted for aortic operation without symptoms of

TABLE 7

IMMEDIATE RESULTS IN PATIENTS WITH BASILAR ARTERY INSUFFICIENCY

Neurologic symptoms	*Deaths*	*No change*	*Improved*	*Asymptomatic*	*Total*
Transient attacks					
Vertebral operation	0	0	0	13	13
Carotid operation	1	4	4	4	13
Persistent progressive					
Vertebral operation	0	0	1	1	2
Carotid operation	2	0	1	0	3
Completed stroke					
Vertebral operation	0	1	1	8	10
Carotid operation	1	1	0	0	2
Vertebral exploration	4	0	1	0	5
Total	8	6	8	26	48

TABLE 8

LATE RESULTS IN PATIENTS WITH BASILAR ARTERY INSUFFICIENCY

Neurologic symptoms	*Deaths*	*No change*	*Improved*	*Asymptomatic*	*Total*
Transient attacks					
Vertebral operation	0	0	0	9	9
Carotid operation	2	3	3	3	11
Persistent progressive					
Vertebral operation	0	0	0	2	2
Carotid operation	0	0	1	0	1
Completed stroke					
Vertebral operation	1	0	1	6	8
Carotid operation	0	1	0	0	1
Total	3	4	5	20	32

cerebral arterial insufficiency. Occlusive lesions were suspected in these cases because of murmurs under the angle of the jaw, and severe partial obstruction was proved by carotid arteriograms. Carotid artery operation was performed first to prevent the development of cerebral arterial insufficiency either during or after major surgery, and the aortic operation was performed at a later date. It is of interest that all 17 patients survived operation and were asymptomatic at the time of discharge from the hospital and that all remain asymptomatic to date except 1 who committed suicide. Of the 49 patients with carotid insufficiency manifested by transient attacks, 46 were asymptomatic at the time of discharge from the hospital; of the 34 patients having operations before January 1, 1960, 31 continue to be asymptomatic. Only 3 patients in this group have died, 1 late from heart disease and 2 early as a result of complications related to the operation. Improvement or complete relief of symptoms occurred during the period of hospitalization in 10 of 12 patients with persistent progressive symptoms from carotid insufficiency. Of the 10 patients operated on before January 1, 1960, 5 were improved and 4 were asymptomatic; 1 patient died after operation, of irreversible brain damage, and only 1 patient remained unchanged.

Most patients in the completed stroke group who had operations for lesions located in the artery opposite the side with symptoms were either improved or became asymptomatic. Of extreme interest is the fact that collateral blood flow provided by operation on lesions in arteries located on the side with symptoms frequently caused improvement. Exploratory operation in patients of this group rarely was associated with improvement.

The results of operation in patients with basilar artery insufficiency were better than in patients with carotid artery insufficiency, particularly when circulation was restored through the vertebral arteries. In general, when operation was performed for lesions of the vertebral artery, most patients were either improved or became asymptomatic, the greatest improvement being obtained in those with the milder symptoms. Increase in collateral blood flow by the removal of carotid artery obstructions in patients with inoperable vertebral artery occlusion appeared in many instances to be associated with definite improvement in the symptoms of basilar insufficiency. Vertebral artery exploration rarely was associated with improvement. Operation for carotid artery obstruction in patients with inoperable vertebral artery obstruction and operations for lesions of the carotid artery on the same side as symptoms from carotid insufficiency appeared to prevent progression of the disease, since fewer deaths occurred in these patients than in those in whom the occluded vessels were only explored. For a more complete and detailed analysis of the functional results of operation, see Tables 5 through 8.

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Incidence of surgically treatable lesions in cases studied angiographically

E. S. Gurdjian, M.D., D. W. Lindner, M.D.,
W. G. Hardy, M.D., and L. M. Thomas, M.D.

DURING THE PAST FOUR YEARS, 800 patients with an admission diagnosis of cerebrovascular disease or a diagnosis of cerebrovascular disease proved after hospitalization have been studied; 489 were male, and 311 were female. The age distribution may be seen in Table 1; 67.5% of the patients were between the ages of 51 and 70.

In Table 2, an analysis of the onset of the ailment is presented. Note that 37% were apoplectic, 15% were slowly progressive, 23% were recurrent and episodic, and 25% were minor, nonfocal complaints. In this series, 772 patients had angiographic studies. Angiography included bilateral carotid angiograms in each instance except in those cases where the diagnosis of a tumor or a mass lesion was made on the first injected side. Percutaneous vertebral angiograms were obtained in 175 instances. During the past year and a half, vertebral angiography by bilateral retrograde brachial injection has been performed in addition to bilateral carotid angiography in 125 patients.

In Table 3, the angiographic findings are analyzed. There are 167 examples of carotid stenosis and 78 of carotid occlusion. Stenosis is seen twice as often as carotid occlusion, as might be expected. Bilateral patchy atheromatous involvement of the bifurcation is also a frequent finding. Brain tumors, intracerebral hematomas, subdural hematomas, aneurysms, and arteriovenous malformations occur fairly frequently in this group because of the way the cases are collected. It must be admitted that, in some cases, the diagnosis is clarified only after definitive studies have been carried out. The shortcomings of angiography are not shown in this table. It is not possible to delineate small artery disease by angiography. Small areas of infarction and death of tissue, which undoubtedly are frequently present in cases of cerebrovascular disease, thus are not shown in this examination.

Let us now consider in more detail 157 of the 167 stenotic lesions shown in Table 3. Table 4 gives the age incidence and mortality in this group; 78% of the patients were between the ages of 51 and 70, and, as one might expect, the mortality is much higher between the ages of 71 and 80. Onset of disability was sudden in 40% of the cases, 11.5% were progressive, 36.3% were episodic, and 11.5% were associated with minor manifestations.

Table 5 tabulates the complaints, signs, and

TABLE 1
AGE AND SEX OF 800 PATIENTS WITH CEREBROVASCULAR DISEASE

Male	489	Female	311
Age		*Age*	
21-30	14	61-70	297
31-40	32	71-80	95
41-50	115	81-90	4
51-60	243		

TABLE 2
ANALYSIS OF ONSET AND COURSE IN 800 PATIENTS

	Total	*Per cent*
Apoplectic	299	37
Progressive	121	15
Recurrent–episodic	181	23
Minor	199	25

symptoms in this group. Onset with unconsciousness is always serious among patients with cerebrovascular disease; 40% died within the first two weeks. Mental changes were noted in 37. Headaches and neck pains were complaints of a total of 3 patients. Syncopal attacks and dizziness were noted in 24, and 36 patients complained of dizziness, not first specified. Convulsions were noted in 9, 5 focal and 4 generalized. Hypertension of more than 170 systolic and 90 diastolic occurred in 95 patients. Hemiplegia occurred in 43 and hemiparesis in 53; 53 had no paralysis whatever. Hemianesthesia or hypalgesia was present in 30. Aphasia or dysphasia was noted in 37 patients, and 11 were dysarthric.

Table 6 lists the associated cerebrovascular lesions in the 157 cases of carotid stenosis. Other associated conditions in these cases are shown in Table 7. In many instances, the contribution of the carotid stenosis to clinical symptomatology was not evident.

Of approximately 800 patients (720 if mass lesions, aneurysms, and arteriovenous malformations are deducted), 36, or about 5% of the total with cerebrovascular disease in our series, were found to be candidates for intimectomy or carotid exploration. In these patients, 26 arteries were treated by intimectomy. The circulation was restored in 20 of the 26; 5 had thrombectomy, 1 had arterial anastomosis, 2 had vertebral intimectomies, 1 had arterial anastomosis, 2 had vertebral exploration, and 1 had a Teflon graft.

In our selection of patients for surgery, we have been guided by clinical signs and symptoms related to the stenotic lesion, the presence or absence of other stenotic or occlusive lesions in the vascular system either in the brain or in the neck, and the presence of occlusive plaques in the carotid artery above the area of stenosis or in the carotid siphon. Usually, the patients were treated with anticoagulants when there were multiple lesions and/or occlusive disease in the carotid siphon or its branches. It was thought that excision of the atheromatous mass at the bifurcation in the presence of such occlusive disease would be useless. Blood in the cerebrospinal fluid and a mass lesion in the cranial cavity were also reasons for not treating the stenotic lesions.

At present, it is difficult to state how many persons between the ages of 55 and 75 without symptoms have stenotic lesions in their carotids—probably quite a few. We need to learn much more about these cases in order to develop an intelligent approach to therapy. We

TABLE 3
ANGIOGRAPHIC FINDINGS IN 772 CASES

Internal carotid stenosis	167 (23%)
Bilateral	65
Proximal anterior cerebral occlusion	85
Vertebral-basilar occlusion	59 (8%)
Intracerebral hematoma	16
Brain tumor	42
Internal carotid occlusion	78 (10%)
Bilateral	9
Middle cerebral occlusion	32
Aneurysm or AV malformation	30
Subdural hematoma	8

TABLE 4
157 CASES OF PARTIAL CAROTID ARTERY STENOSIS

No.	*Age*	*% total*	*Number died*	*% total deaths*	*% age group died*
1	Under 41	0.6	0	0	0
8	41–50	5.1	0	0	0
57	51–60	36.3	16	33.3	28.1
66	61–70	42.0	22	45.8	33.3
25	71–80	15.9	10	20.8	40.0

Male: 97 (3 Negro) Female: 60 (1 Negro)

TABLE 5
CAROTID ARTERY STENOSIS (157 CASES)

Unconscious onset	19	Hemiplegia	43
Mentally affected	37	Hemiparesis	53
Dizziness	36	Monoplegia	2
Syncopal attacks	12	Monoparesis	5
Dizziness and		Quadriparesis	1
syncopal attacks	12	No paralysis	53
Headaches	31	Hemianesthesia	
Neck pain	5	and/or hypalgesia	30
Headaches and		Paresthesia	25
neck pain	2	Dysphasia	20
Field defects	8	Aphasia	17
Convulsions	9	Dysarthria	11
Hypertension	95		

TABLE 6
ASSOCIATED CEREBROVASCULAR LESIONS IN 157 CASES OF CAROTID STENOSIS

Complete carotid occlusions (contralateral)	11
Middle cerebral trunk occlusions	10
Middle cerebral small artery occlusions	9
Anterior cerebral occlusions	17
Generalized cerebral arteriosclerosis	9
Vertebral-basilar stenosis	4
Vertebral occlusion	11
Subarachnoid hemorrhage (no aneurysm proved)	4

TABLE 7
ASSOCIATED CONDITIONS IN 157 CASES OF CAROTID STENOSIS

Diabetes	9	Parkinson's disease	3
Cardiac disease	16	Trigeminal neuralgia	1
Renal disease	1	Bleeding peptic ulcer	3
Cardiorenal disease	2	Tuberculosis	1
Peripheral vascular disease (occluded iliacs)	1	Aneurysm, right internal carotid	1
Intracerebral hematoma	3	Aneurysm, right subclavian	1
Meningioma	1	Syphilis	2
Metastatic brain tumor	1	Tinnitus only	1
Subdural hematoma	1		

would urge good lateral views to include the neck when angiography is used for other diagnostic problems such as brain tumor and head injury. We may thus be able to collect additional data on the incidence of these asymptomatic partial occlusions.

The fact that there may be multiple lesions and incidental disease cannot be denied. We have examples of the combination of stenotic lesions at the carotid bifurcation, bloody spinal fluid, intracerebral hematoma, and extensive atherosclerosis of the circle of Willis and the vertebral-basilar system in the same case. We have had further examples of a stenotic arterial lesion on the same side with a huge subdural hematoma.

A case report will illustrate these points. At the age of 57, the patient was admitted to the hospital in an unconscious state with left hemiplegia. Angiography showed a partial occlusion of the right carotid at the bifurcation involving the internal carotid artery. The anteroposterior view of the angiogram suggested some bowing of the anterior cerebral to the left, but this was thought to be due to edema, possibly because of occlusive disease of the right carotid. The cerebrospinal fluid was clear. The right carotid artery was explored, and a scar across the internal carotid was found to cause the stenosis. Nothing more was done to the artery. After the operation, the patient improved. The paralysis of the left half of the body disappeared, and he went home feeling quite well and remained so until eight months later. He returned again unconscious with left hemiplegia. Angiograms now revealed no partial occlusion. The anterior cerebral was more displaced than previously. A parasagittal meningioma was removed. Again, the patient improved and has now been well for a year and a half. The finding of a stenotic lesion may be deceptive. We now believe that the patient had postictal paralysis, caused by the tumor, for which he was hospitalized on both occasions. The first attack was mistaken for cerebrovascular insufficiency due to a coincidental right internal carotid stenosis which was undoubtedly benign and unrelated to his symptoms.

The natural history of internal carotid and vertebral-basilar artery occlusion

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and Sigmund Groch, M.D.

IT IS SURPRISING how little is known of the natural history of disease. Cerebrovascular disease is one of the most commonly encountered of all disease states, yet, at a time when it has become necessary to compare the results of recent suggestions for therapy with the natural evolution of the disease, we find ourselves unable to do so. Often our interest in a particular disease state is first prompted by a promising trial of a new therapy and, second, by general interest in the disease itself. Also, the eagerness to treat ill persons and the zeal with which such new therapy is often applied makes it even more difficult to illuminate clearly the natural history of disease processes.

We have evaluated the history and course of 57 patients with carotid artery occlusion demonstrated either by arteriography or autopsy and of 50 patients with clinically unequivocal evidence of occlusion in the vertebral-basilar arteries or one of their major branches. The patients have been drawn from two sources: the New York Hospital and the Cornell Medical and Neurological Services of Bellevue Hospital. Most of the information is incomplete and inconclusive, but enough is available to give some idea of the natural history of these disorders.

TABLE 1
AGE AND SEX INCIDENCE

Age	*Carotid occlusion*	*Vertebral-basilar occlusion*
	39 Males 18 Females	33 Males 17 Females
0-10	1	0
11-20	0	0
21-30	0	0
31-40	3	1
41-50	10	5
51-60	17	18
61-70	17	18
71-80	6	7
81-90	3	1
Total	57	50

Table 1 shows the age and sex incidence of both groups of patients. Males are more frequently affected than females in a ratio of about 2 to 1. Carotid artery occlusion occurs most often in persons 41 to 70 years of age, while vertebral-basilar artery occlusion develops about one decade later in persons 51 to 70 years. While carotid artery occlusion is occasionally encountered in patients below the age of 30, clinical vertebral-basilar artery occlusion in this age group is rarely described.

Table 2 shows that many of the patients had evidence of other diseases, usually vascular, in other parts of the body. A relatively small number of patients had no associated disease. The most commonly encountered associated disorder in both groups was hypertension. Diabetes appears to be slightly more common in those with vertebral-basilar occlusion. There is a high incidence of previous cerebrovascular accidents in both groups.

It is well known that many patients in whom carotid or vertebral-basilar occlusion develops often have transient episodes of neurologic dysfunction before permanent neurologic defects develop. Such attacks are of importance as warnings of further and perhaps permanent difficulty. Table 3 shows that such episodes occurred in a little less than half of all the patients. In about half of these, such warnings began at least six months before permanent neurologic disability. All occurred

TABLE 2
FREQUENCY OF ASSOCIATED DISEASES

Associated diseases	*Carotid occlusion*	*Vertebral-basilar occlusion*
Hypertension	23	32
Diabetes	5	12
Arteriosclerotic heart disease	16	9
Previous cerebrovascular accidents	15	10
Rheumatic heart disease	4	2
No associated disease	2	7

TABLE 3
DURATION OF INTERMITTENT ISCHEMIC ATTACKS BEFORE DIAGNOSIS

Duration	*Carotid occlusion*	*Vertebral-basilar occlusion*
Over 48 months	2	0
48-37 months	0	1
36-25 months	3	0
24-13 months	5	3
12- 7 months	2	6
6- diagnosis	11	13
Total	23	23

long enough before the patient arrived in the hospital to have allowed the institution of effective preventive therapy (if such therapy were available). If, in addition to patients with transient episodes of neurologic dysfunction, we include those with a previous stroke, then 38 patients with internal carotid artery occlusion and 33 patients with vertebral-basilar artery occlusion had prior warnings of the events leading to diagnosis.

Table 4 shows the severity of the stroke, graded as mild, moderate, and severe, and the incidence of each in patients with the two varieties of occlusion. Severe strokes were more common in carotid occlusion.

The difference in the incidence of severe and moderate defects in the two groups may result from the fact that carotid artery occlusion involves one vessel and vertebral-basilar system occlusion involves many. Indeed, the latter is actually a multiple syndrome complex, the severity of which depends upon the level of the brain stem involved and upon whether the lesions are dorsal or ventral. The patients in the vertebral-basilar artery group with severe neurologic defects all had ventral midbrain stem dysfunction bilaterally with and without evidence of extension to the more dorsal portions of the brain stem. Among those with moderate neurologic defects, most had unilateral lesions either dorsally or ventrally located. Clearly defined syndromes associated with presumed occlusion in a branch of the vertebral-basilar system, such as the posterior inferior cerebellar artery, were rarely encountered in our patients.

In both series of patients, some were treated with anticoagulants. Some of the patients with internal carotid artery occlusion were treated by cervical ganglionectomy.

Figure 1 shows what we know of the history of 40 patients with carotid artery occlusion who received no specific therapy.[1] A striking feature of the natural history of this group is the variability of symptoms and their duration before the diagnosis of occlusion was made. The duration of transient attacks of neurologic dysfunction before evidence of permanent neurologic defects makes the evaluation of therapy of these episodes difficult and points up again the need for controls in evaluating therapy.

Fourteen patients died during their hospitalization, an initial mortality rate of 35%. The average duration of follow-up of the survivors after diagnosis has been two years. Two more deaths have occurred, the first before one year of follow-up was completed and the second before two years. The cause of death was the initial stroke in 12, a second stroke in 1, and coronary artery disease in 3.

Of the 26 survivors of the initial stroke, 9 had transient attacks of neurologic dysfunction. In 5, they stopped spontaneously without

TABLE 4
SEVERITY OF NEUROLOGIC DEFECTS AT DIAGNOSIS

	Carotid occlusion	*Vertebral occlusion*
Severe	23	16
Moderate	9	25
Mild	19	9
No neurologic defect	6	0

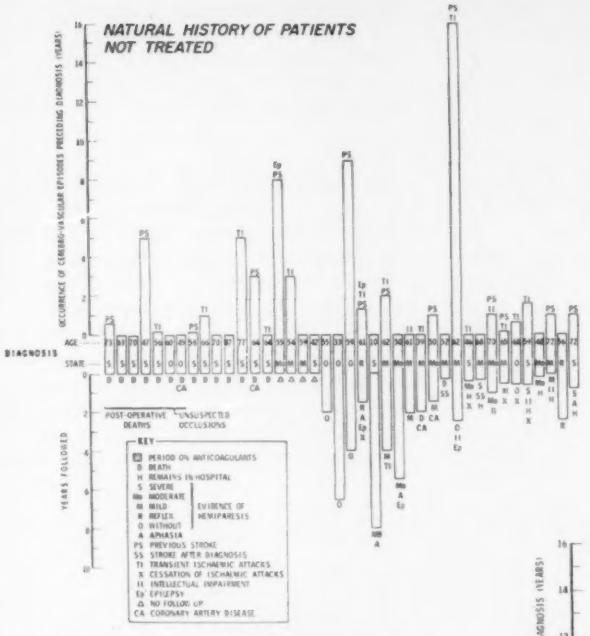

Fig. 1. History of 40 patients with carotid artery occlusion who did not receive specific therapy

therapy; 5 required permanent hospitalization. The remainder were home or at work.

Figure 2 shows the course of 17 patients in the treated group. The death rate in this group is low, but these patients were chosen for therapy after 90% of the deaths in the whole group had already occurred. Transient ischemic attacks disappeared in 3 of 4 patients on anticoagulant drugs and in 3 of 6 patients who had cervical ganglionectomy.

Figure 3 shows the natural history of 32 patients with clinically evident vertebral-basilar artery system occlusive disease who received no specific therapy. There were 16 deaths in this group. Of these, 8 occurred within one month after diagnosis, 6 were due to the stroke, 1 to congestive heart failure, and 1 to myocardial infarction. In the next six months, 5 more patients died, 4 of the initial stroke and 1 of congestive heart failure. In the following year, 3 more patients died as a result of a second stroke. The mortality rate for one month was 25%; for six months, 45%; for one year, 50%; and for one and one-half years, 60%. These figures show, in addition, that if the

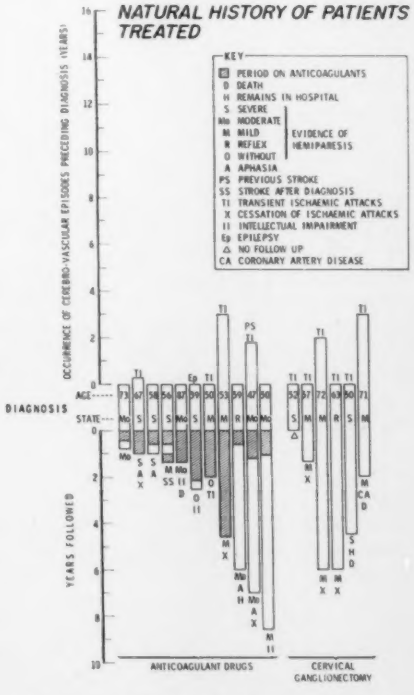

Fig. 2. Course of 17 patients treated with anticoagulant drugs or cervical ganglionectomy.

patient survives the initial event for six months, his outlook for recovery is good but that he has a fair chance of suffering a repeated stroke.

The average duration of follow-up for the survivors is one and one-half to two years. Half of these patients are incapacitated and half of them are not. When all of the patients have been followed this long, the mortality rate will undoubtedly be higher. The location and size of the brain stem lesion has considerable bearing on the immediate prognosis. Those patients with midbrain stem lesions involving both sides of the ventral and dorsal brain stem had severe strokes, and the mortality rate was highest in this group.

Figure 4 shows the course of 18 patients who were treated with anticoagulant drugs for forty-eight hours to one and one-half years. There were 3 deaths among these patients, 2 of congestive failure and 1 after surgery for gangrene of the foot. No comparisons between the treated and untreated groups can be made, but the absence of repeated strokes in patients while on anticoagulant therapy is interesting.

COMMENT

From the data presented, a few generalizations about the natural history of carotid and vertebral-basilar system occlusion can be made. Both disorders occur more often in men than in women, developing most frequently after 40 and before 80 years of age, with vertebral-basilar occlusion reaching its peak about a decade after internal carotid artery occlusion. Both have a high incidence of associated diseases, with hypertension and diabetes being most commonly encountered. Both conditions are associated with a high incidence, about

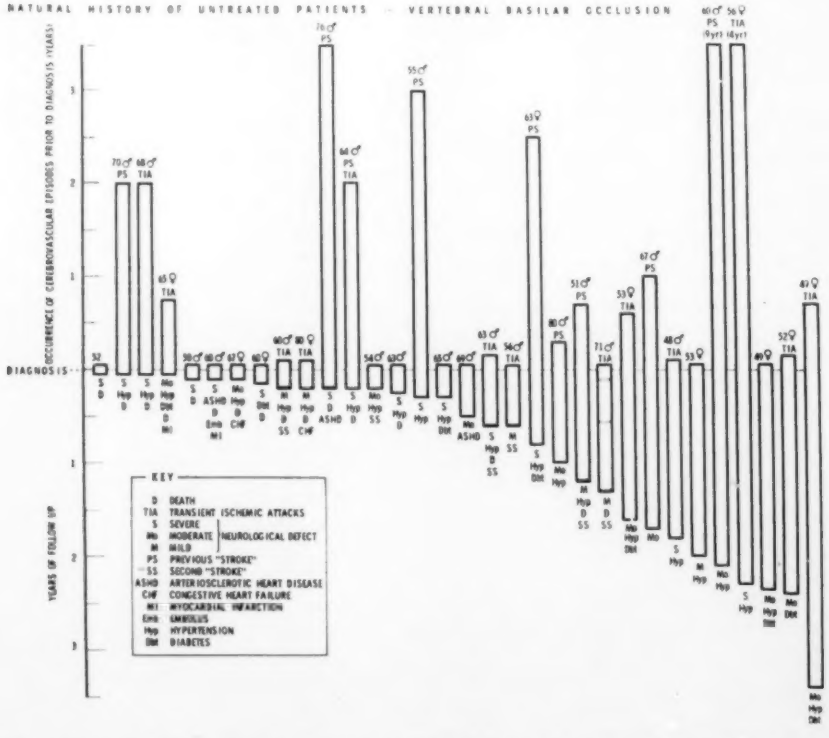

Fig. 3. History of 32 patients with vertebral-basilar artery system occlusive disease who did not receive specific therapy.

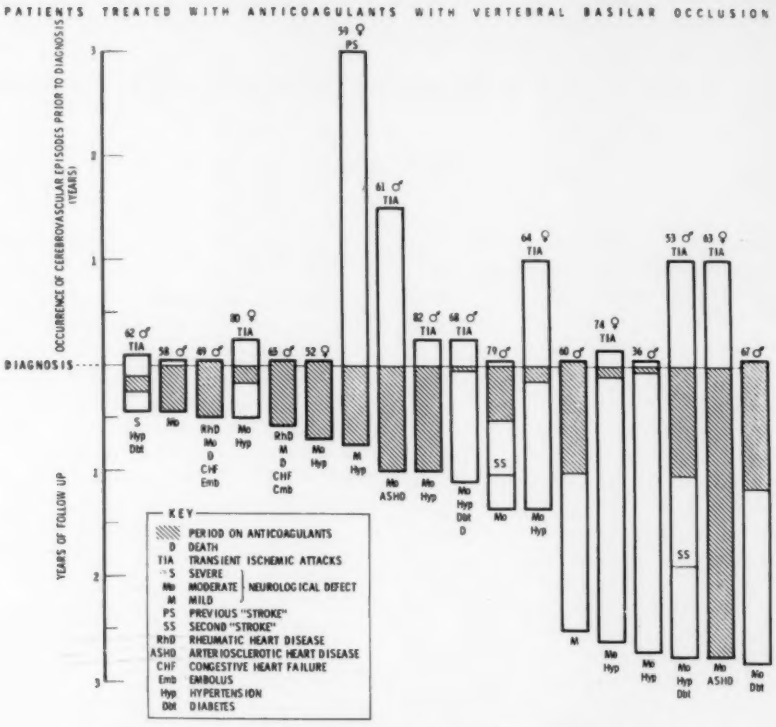

Fig. 4. Course of 18 patients treated with anticoagulant drugs.

50%, of intermittent attacks of neurologic dysfunction beginning a few days to a few years before the diagnosis of occlusion is made. Sudden onset without warning occurs in about 50% of both groups. Severe dysfunction in patients who survive appears to be more common in carotid occlusion than in vertebral-basilar occlusion. The initial and one-year mortality from the stroke is higher in vertebral-basilar occlusion than in carotid artery occlusion, and, indeed, the prognosis for life is generally better in internal carotid artery occlusion. When transient intermittent ischemic attacks occurred prior to diagnosis of carotid occlusion, they stopped in the untreated groups as often as they did in the treated groups. The follow-up history of both groups of patients is associated with a high incidence of myocardial infarction and congestive heart failure. Disability in the survivors appears to be less marked in those patients with vertebral-basilar occlusion, probably due to absence of aphasia and because these survivors often have small lesions which are more easily compensated.

Obviously, if therapy is to be maximally effective, it must be instituted during the warning phase of the disorder as manifested by transient attacks of neurologic dysfunction or by a gradual onset. It is also clear that results of therapy applied during this period can only be compared with patients similarly affected and not given therapy. Any therapy which reduces the high initial mortality and incidence of a second stroke or other thromboembolic phenomena is desirable. Again, evaluation must be based on arbitrarily selected control patients.

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Posterior communicating aneurysms

Lawrence S. Walsh, M.B., F.R.C.S.

THIS REPORT gives a brief account of the first definite results obtained from a clinical trial of surgical and nonsurgical methods of treatment of ruptured intracranial aneurysms.

This study was started in January 1958 and was mainly conducted at the Neurosurgical Department of St. George's Hospital, Wimbledon, England.

METHOD OF INVESTIGATION

After routine clinical examination, a lumbar puncture was performed, unless this had already been done. Each common carotid artery was compressed in turn for ten minutes. If the patient did not withstand compression on either side, immediate angiography was deferred for a day or two. If compression was tolerated, bilateral carotid angiography was performed immediately. If no aneurysm was shown, vertebral angiography was performed two days later. Those patients in whom an aneurysm was shown were then reviewed, and an immediate decision as to its operability was made. If the lesion was considered operable, the patient was included in the trial. The following types of patient were excluded from the trial:

TABLE 1

	Over 50 years	*Under 50 years*
Operation	28	18
Nonsurgical	29	19

TABLE 2
HYPERTENSION

	Hypertensive	*Nonhypertensive*
Operation	21	25
Nonsurgical	21	27

Patients were considered to be hypertensive if their blood pressure was 160/90 mm. Hg or above.

1. Patients dying before the investigation could be completed

2. Those with multiple aneurysms in whom there was no evidence as to which aneurysm had bled and in whom the aneurysms demonstrated could not be treated by a single operation

3. Patients with evidence of a large intracranial hematoma which appeared to be threatening the life of the patient. Such patients were all treated surgically.

4. Patients with aneurysms which were thought to be inaccessible or for other reasons inoperable.

The patients who were included in the trial were grouped according to the site of the aneurysm, whether normotensive or hypertensive, and above or below 50 years of age. They were also subdivided into 2 clinical categories:

Category A. Patients in danger of dying in the immediate future from the hemorrhage causing admission to the hospital. This category included all those in coma or a semiconscious state with marked neurologic signs.

Category B. Patients who had recovered from the hemorrhage, completely or in part, and were not in danger of dying from this hemorrhage. In these patients, the risk was only from further hemorrhage.

Finally, they were subdivided according to the time of inclusion in the trial, in relation to the hemorrhage responsible for their admission to hospital. By this stratification, the patients were then chosen for nonsurgical or surgical treatment by random selection.

TREATMENT

The patients chosen for nonsurgical treatment were transferred, as soon as their clinical state permitted, back to the admitting hospital, and it was recommended that they be given

six weeks' total bedrest. The patients chosen for surgical treatment were operated upon at once. All surviving patients were assessed by a neurologist six months after their hemorrhage.

Toward the end of 1959, it became evident that the difference between the surgically and conservatively treated patients in the internal carotid and posterior communicating group showed a significant advantage in favor of surgical treatment, so these patients were no longer included in the trial and are now all treated surgically. It is the results in this group that I now want to discuss. This group includes all aneurysms on the intracranial internal carotid artery below its bifurcation, most of them being near the point of origin of the posterior communicating artery.

PATIENTS INCLUDED IN TRIAL

During the period January 1, 1958, to August 31, 1959, 117 patients with an aneurysm of this type were admitted to the hospital; 23 of these were excluded from the trial, and the remaining 94 were included. Of this number, 48 were treated nonsurgically and 46 surgically. The 23 patients were excluded for the following reasons: 2 died before investigation; 1 had negative arteriograms, but autopsy showed an aneurysm; 12 had intracerebral hematoma and were treated surgically; 2 had inoperable lesions; 6 were seen more than two months after the incident, and, in some, the subarachnoid hemorrhage had not been verified by lumbar puncture.

Tables 1 through 4 show the various subgroups which I have mentioned and the number of patients in each.

RESULTS OF TREATMENT

Table 5 shows the mortality in the various subgroups of the 48 medically treated patients. This shows the marked influence of clinical status on mortality. With regard to the cause of death, in category A, 2 patients deteriorated and died and the remaining 3 suffered recurrent hemorrhage from which they died. In category B, all 15 patients died of recurrent hemorrhage.

There were in all 24 instances of recurrent hemorrhage in the 48 patients—3 in category A, all of whom died, and 21 in category B, of whom 15 died.

Table 6 shows the time of the 24 recurrent hemorrhages.

Before admission, 36 patients had had 1 hemorrhage, 8 had had 2, and 4 had had 3.

Table 7 shows the duration of bedrest in the survivors.

TABLE 3
CLINICAL CATEGORY

	Category A	*Category B*
Operation	5	41
Nonsurgical	6	42

TABLE 4
INTERVAL BETWEEN SUBARACHNOID HEMORRHAGE AND ADMISSION TO TRIAL

	1-3 days	*4-6 days*	*7-13 days*	*Over 13 days*
Operation	23	8	10	5
Nonsurgical	25	7	12	4

TABLE 5
PATIENTS TREATED NONSURGICALLY

	Total cases	*Deaths*
Over 50	29	10
Under 50	19	10
Hypertensive	21	8
Normotensive	27	12
Category A	6	5
Category B	42	15
1-3 days	25	11
4-6 days	7	4
7-13 days	12	4
Over 13 days	4	1

TABLE 6

0- 6 days	5 cases	3 deaths
7-10 days	7 cases	6 deaths
10 days or more	12 cases	9 deaths

TABLE 7

Bedrest for 1-2 weeks — 3 cases
Bedrest for 2-4 weeks — 6 cases
Bedrest for 4-6 weeks — 21 cases

TABLE 8
46 PATIENTS TREATED SURGICALLY

	Total cases	*Deaths*
Over 50	28	7
Under 50	18	2
Hypertensive	21	7
Normotensive	25	2
Category A	5	5
Category B	41	4
1-3 days	20	3
4-6 days	7	1
7-13 days	9	0
Over 13 days	5	0

No case of recurrent hemorrhage appears to have occurred as a result of premature mobilization or of transfer of the patient from one hospital to another.

Surgically treated patients. Table 8 shows the higher mortality in the older age group and in the hypertensive patients. The importance of the clinical category is again obvious. Until the end of the first week, there is not much change in the operative mortality but these figures are obviously very small.

TABLE 9
TYPE OF OPERATION

	Category A	*Category B*
Total	5	41
Craniotomy	5	4
Deaths	5	1
Per cent	100	25
Carotid ligation	—	37
Deaths	—	3
Per cent	—	8

TABLE 10

	Category A		*Category B*	
	Surgically	*Non-surgically*	*Surgically*	*Non-surgically*
Total	5	6	41	42
Craniotomy	5	6	4	1
Death	5	5	1	0
Per cent	100	83	25	
Carotid ligation	—	—	37	41
Death	—	—	3	15
Per cent			8	36

Those who withstood carotid compression in the neck for ten minutes were treated by carotid ligation. Those who did not were treated by craniotomy with clipping of the neck of the aneurysm (Table 9).

Table 10 shows a comparison of the results of surgically and nonsurgically treated patients, the latter patients being grouped according to the operation for which they would have been suitable.

Surgical treatment has not benefited the patients in category A, but the mortality in category B is much lower for the surgically treated than the nonsurgical group. This difference, 9.8% against 35.7%, in this number of patients is of a high degree of significance, which is almost entirely due to the low mortality for the patients treated by carotid ligation.

Cause of death in the surgically treated patients. The 5 patients in category A who died continued to show deterioration after operation. The 4 deaths in category B were the result of the operation, 3 of the patients having ischemia of the hemisphere supplied by the ligated common carotid artery. None of them had recurrent hemorrhage, and there were, in fact, no recurrences of hemorrhage in the surgically treated patients.

Complications following carotid ligation. Of the 37 patients in category B treated by carotid ligation, 10 had postoperative hemiplegia or hemiparesis associated with dysphasia when the dominant hemisphere was affected. Considering the time of operation in relation to the incidence of complication does not show any reduction in frequency until fourteen days after hemorrhage. Half the patients were hypertensive; this factor does not appear to be of significance. Age, however, appeared significant, since 8 of 10 patients with complications were over 50 years of age. Of these 10 patients, 3 died; all 3 were over 60 years of

TABLE 11

	Operation	*Conservative*
Full work	29	19
Partially disabled	6	6
Totally disabled	2	2
Alive but condition unknown	–	1

age, and all were operated on within one week of hemorrhage. Of the 7 survivors, 3 showed some recovery.

Fate of survivors. Table 11 shows a comparison of the status of the survivors in the surgically and the conservatively treated groups, the morbidity rate in the surgically treated cases being less than in the nonsurgically treated patients. It is true, however, that most of the disability in the surgically treated group was caused by complications of the operations.

In conclusion, then, we believe that a comparison of the results of treatment in the 2 groups shows that surgical treatment is superior in the category B patients. However, there are many questions still to be answered, such as the relative merits of craniotomy and carotid ligation and the optimum time after hemorrhage for operation. These problems and others are being studied, and we believe that it is by such planned trials as this that they are likely to be solved.

Cooperative clinical study of intracranial aneurysms and subarachnoid hemorrhage

Aneurysm Study Group

Presented by Herbert Locksley, M.D.

THIS COOPERATIVE STUDY is sponsored by the United States Public Health Service through the National Institute of Neurological Diseases and Blindness. It represents the combined efforts of 20 university neurologic and neurosurgical centers in the United States and 1 in England to study pressing clinical and research questions relative to subarachnoid hemorrhage and certain other aspects of cerebrovascular disease. This Cooperative Study was conceived at a meeting of an ad hoc committee called together by the NINDB in Bethesda in October 1956. It seemed evident that no single investigator or clinic was likely to accumulate enough clinical cases to resolve definitively the unsatisfactory state of information regarding questions of management and therapy which arise so urgently in patients presenting with subarachnoid hemorrhage and aneurysm. It was proposed therefore by the ad hoc committee that many of the inconsistencies, and even antitheses, evident in the literature might be resolved through a general agreement regarding terminology, criteria for evaluation of patients, characterization of indications for various modes of treatment, and adoption of a uniform method of case reporting.

A general plan for a Cooperative Study was evolved at this meeting of the ad hoc committee. At subsequent planning sessions, a Study group was organized and a Central Registry established in May 1957. As now constituted, the 20 participating centers are represented nearly equally by medical neurologists and neurosurgeons.

CENTERS AND INVESTIGATORS

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Cornell University, New York Hospital: Bronson S. Ray, M.D.; Bellevue Hospital: Fletcher McDowell, M.D.

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Harvard University (Massachusetts General Hospital): William H. Sweet, M.D., C. Miller Fisher, M.D.

University of Indiana: William DeMyer, M.D., Alexander T. Ross, M.D.

State University of Iowa: A. L. Sahs, M.D., Russell Meyers, M.D., George Perret, M.D., Herbert Locksley, M.D.

University of London (St. George's Hospital): Wylie McKissock, F.R.C.S.

University of Louisville: Ephraim Roseman, M.D., Taha Anvari, M.D.

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Mount Sinai Hospital, New York: Mortimer F. Shapiro, M.D., Paul Slosberg, M.D.

University of Pennsylvania: George D. Gammon, M.D., James F. Toole, M.D.

University of Tennessee: Francis Murphey, M.D.

Washington University (Barnes Hospital): William S. Coxe, M.D., Henry Schwartz, M.D.

Wayne State University: Elisha S. Gurdjian, M.D.

Operation of the Central Registry, which is located at the State University of Iowa in Iowa City, is supervised by a committee under the direction of Dr. A. L. Sahs. Statistical

aspects of the Study are supervised by the Department of Mathematics and Biostatistics at the University, and the encoding of data on IBM cards and machine analysis of the data are carried out by the State University of Iowa Statistical Center.

The Study has addressed itself to getting the best possible answers to a number of questions. Some of these are of broad interest:

1] The causes of spontaneous subarachnoid hemorrhage (excluding trauma) and their relative incidence

2] The "natural history" of intracranial aneurysms and cerebral arteriovenous malformations

3] The prognosis after subarachnoid hemorrhage of nonsurgically treated aneurysms in the various principal locations, with calculations of survival probability at various periods after the initial bleeding episode

4] The clinical course and prognosis of patients with subarachnoid hemorrhage due to various other definable causes, as well as those in whom no specific lesion is demonstrable by angiography and the cause of hemorrhage remains obscure

5] The influence on prognosis of factors such as age, arterial hypertension, site of aneurysm, and "state of consciousness."

Other questions are of immediate practical value:

1] The optimal time for performance of angiography

2] Evaluation of various types of surgical therapy

3] The optimal time for surgery

4] The influence of age and site of lesion

5] The value of various adjuncts to surgery, such as hypothermia, hypotensive agents, and temporary vascular occlusion.

There is a great need for long-term follow-up data, with evaluation of patients' functional disability as well as the incidence of survival.

Finally, the Study offers participants the opportunity to investigate cerebrovascular dynamics under a variety of conditions, and it is conceivable that these ancillary studies may yield information quite as valuable as that from the main clinical study.

The first task undertaken was to prepare a set of protocol forms to be used by the participants for case reporting and follow-up studies. The protocol is, in a sense, the heart of the study. It attempts to incorporate in codable form all available data which might be needed to answer pertinent questions and represents much critical thought and discussion by subcommittees and individuals of the group. The protocol consists of 6 bound fascicles dealing separately with [1] history and physical findings, [2] angiographic findings, [3] surgical treatment, [4] nonsurgical treatment, [5] pathologic findings, and [6] follow-up information. Completed protocols began arriving at the Central Registry in January 1958, and there are now over 1,300 cases on file with the data encoded on punch cards.

The statistical desirability of having the case material rigorously randomized with regard to selection for various modes of treatment was recognized in the planning stages of the Study. How to achieve this provoked much thought and animated discussion in the group, but, in the end, it did not prove possible to arrive at a general policy of random selection suitable to the requirements and desires of the various centers and investigators. Randomization has thus been left to the discretion of each group with the expectation that this factor will become less important as the series grows. However, the subsequent addition to the Study of the London group under Mr. Wylie McKissock has been a fruitful step toward randomization because they have been able to establish a program of alternate selection of cases for surgical and nonsurgical therapy applied to a large population of patients with subarachnoid hemorrhage.

The 1,300 cases already accumulated at the Central Registry constitute a large series by most standards. However, when the total number is broken up into appropriate categories and matched with controls, the number of cases pertinent to analysis of many specific questions is as yet too small to provide statistically valid conclusions—particularly as regards treatment and prognosis. It is currently felt that the duration of the Cooperative Study should be such as to provide statistically adequate figures for most if not *all* of the

questions posed in various areas of the over-all problem. This is likely to require a total of at least 5,000 cases of subarachnoid hemorrhage and possibly as many as 10,000. A follow-up period of five years after the initial hemorrhage would certainly be considered minimal for fashioning a good prognostic yardstick and a dependable baseline for relative evaluation of various current modes of treatment as well as for those that may be expected to develop in the near future. Ideally, the follow-up study should encompass the patient's lifetime. In practice, the duration of the Cooperative Study will undoubtedly reflect a reasonable compromise of objectives, heavily influenced by the availability of funds for its continuance.

As for publications, each participant of course exercises free right to the data of his own cases. However, it has been agreed by the group that the results of data analysis at the Central Registry shall be published only with the assent and authorship of the Cooperative Study. Significant data and interpretations will be published as they emerge, and it is planned, ultimately, to publish the overall Study in monograph form.

Nonaneurysmal intracranial hemorrhage

H. H. Hyland, M.D.

THE SUBJECT OF nonaneurysmal intracranial hemorrhage covers a large field, and, in the time at my disposal, I can mention only a few aspects of the problem. Cerebrovascular disease with hypertension is by far the most common cause. Russell[1] surveyed 461 autopsy cases of massive cerebral hemorrhage at the London Hospital from 1912 to 1952 and found 232, or 50%, due to this cause, while ruptured congenital aneurysms were responsible in about 20% of cases.

There is general agreement that hypertensive cerebral hemorrhage is likely to be rapidly fatal, the majority of patients dying within two weeks.[2] However, with the widespread use of anticoagulant therapy in recent years, it is important to keep in mind that nonfatal intracerebral hemorrhage may occur in hypertensive patients, and, in some instances, the clinical distinction from softening may be difficult. Hudson and I[3] reviewed autopsies of 100 cases of hypertensive vascular disease. While cerebral hemorrhage was the cause of death in 31, it was of interest that in 10 cases the brain revealed a hemorrhage of significant size—1 to 3.5 cm. in diameter— which had not caused death. The interval between these hemorrhages and death from other causes varied from six weeks to three years. The hemorrhages were all situated in the cerebral hemispheres, with extension to a ventricle in 5 instances. Figure 1 shows the lesion in 1 of these cases, in which death was from an extracranial cause, the hemorrhage having occurred three months previously. Cases similar to the remaining 5, in which bleeding had not extended to the ventricles, are likely to present a particularly difficult problem in distinguishing hemorrhage from infarction, since the cerebrospinal fluid would probably not contain blood.

In addition to these large, nonfatal hemorrhages, small lesions showing histologic characteristics of old hemorrhage that can be correlated in time and situation with previous transitory symptoms are occasionally found at autopsy in hypertensive patients. Such symptoms, which sometimes consist of brief hemiparetic manifestations, may resemble those accompanying internal carotid or basilar insufficiency.

Angiomatous malformations rank third in frequency as the cause of spontaneous intracranial hemorrhage. A recent review of 55 clinically verified cases from the Toronto General Hospital files in the past twelve-year period shows hemorrhage as the presenting symptom in 31. It was the first manifestation of the lesion in 23 instances, 7 of which gave indications in the history of one or more previous bleeding episodes. In the remaining 8 patients, epilepsy or headache preceded the hemorrhage by months or years. Similar observations regarding the frequency of hemorrhage from these lesions have been reported by others.[4,5] Although hemorrhage may occur

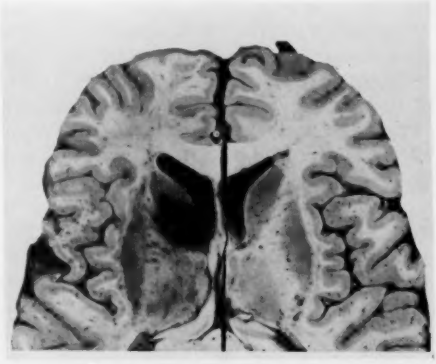

Fig. 1. Three-month-old nonfatal hemorrhage into left caudate nucleus and internal capsule, with slight intraventricular extension. (Reproduced by courtesy of *Annuals of Internal Medicine.*)

Fig. 2. Asymptomatic angiomatous malformation infiltrating cortex and subcortical white matter of right temporal lobe, an incidental finding at autopsy.

at any age, the initial episode is most common in the second and third decades, the average age being considerably younger than with hemorrhage from aneurysms.[4–9] The size of these vascular anomalies does not seem to determine whether hemorrhage will occur or whether the outcome will be fatal. Margolis and associates[10] and Crawford and Russell[7] have shown that very small malformations can cause massive fatal hemorrhage, and it is evident that such lesions could be destroyed by hemorrhage so they might not be recognized on an angiogram or even at autopsy.

I have recently reviewed our autopsy material of the past twenty-five years, finding 101 patients with verified angiomatous malformations in the cerebral hemispheres, cerebellum, and brain stem. There were 37 with massive hemorrhage; in several, no underlying lesion was immediately obvious, but a meticulous search by the pathologist revealed a few abnormal vascular channels in the wall of the hemorrhagic cavity or in the blood clot which indicated an angiomatous malformation as the cause. In 57 patients, the lesions were incidental findings at autopsy. These malformations were all small, and the histories did not reveal any symptoms that could be attributed to them, although 8 had pathologic evidence of old, localized hemorrhage. One such incidental lesion, from a 64-year-old diabetic patient who died from myocardial failure, is seen in Figure 2. The abnormal vessels were found to have degenerated, irregular walls and to be surrounded by histiocytes containing blood pigment that indicated a previous small hemorrhage. Odom, Bloor, and Woodhall[9] have pointed out that patients with cerebral hemorrhage caused by verified angiomatous malformations differ clinically in no significant way from young persons in whom the etiology has not been determined at operation or at autopsy. This was our opinion, also, when studying spontaneous cerebellar hemorrhage,[11] and it is probable that, in many cases of intracranial hemorrhage for which no cause is found, bleeding follows rupture of small angiomatous malformations similar to that shown in Figure 2 and which may have been so damaged by the bleeding that they escape recognition.

Occasionally, the risk of massive hemorrhage from small angiomatous malformations may be averted through spontaneous healing. Figure 3 shows a vascular malformation in the precentral gyrus of a man aged 70, who had occasional epileptic seizures over many years. Large amounts of phagocytosed blood pigment surrounded the poorly formed vascular channels, many of which were thrombosed and contained calcium in their walls. Old

Fig. 3. Angiomatous malformation in region of right precentral gyrus, in which circulation was practically obliterated as a result of old thrombus and hemorrhage.

thrombus, together with hemorrhage, had practically obliterated the circulation through the vessels of the malformation.

With the more general use of angiography in diagnosis and study of angiomatous malformations, there is mounting evidence that a larger proportion of patients will survive intracranial hemorrhage from this cause than will survive a ruptured aneurysm.[4,5,8] In our series of 31 patients with hemorrhage, 24 survived, of whom 15 had surgical treatment. The location of the lesion is very important in prognosis, since this determines its amenability to surgery and also the chance of survival. Massive hemorrhage from malformations deep in a hemisphere or in the cerebellum can be rapidly fatal. If the substance of the brain stem is the site, hemorrhage of any size is likely to cause death. With lesions on or close to the surface of the brain, the outlook is better, and some patients survive repeated hemorrhages in this situation.

A number of other disorders may cause nonaneurysmal intracranial hemorrhage,[12] but, in some, the occurrence of hemorrhage is of pathologic interest only. It is not possible to discuss all these conditions here, but I would like to make brief reference to 3 that may be important.

Occasionally, with blood diseases such as leukemia and thrombopenic purpura, massive bleeding may be confined to the brain. It may even be the first or a very early manifestation of the disease.[11] The possibility always needs to be considered in young persons with otherwise unexplained cerebral hemorrhage. Blood examination is mandatory in such cases.

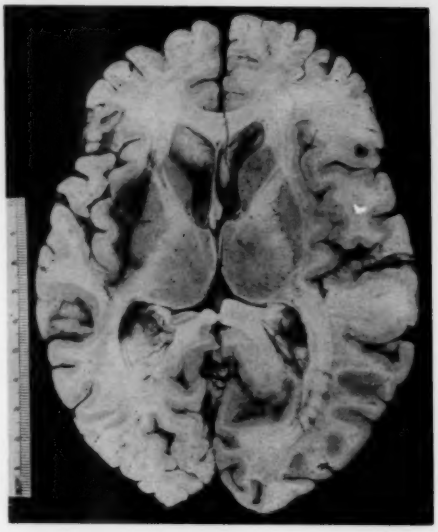

Fig. 3. Four-month-old linear hemorrhage in left external capsule which arose from rounded necrotic metastasis seen in the center. Primary carcinoma was in the kidney.

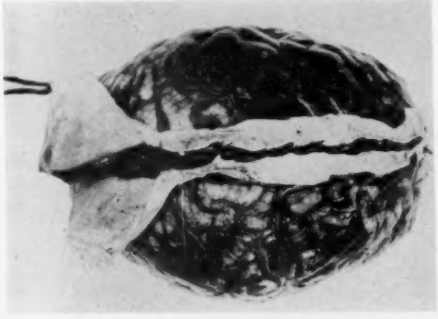

Fig. 4. Extensive subarachnoid hemorrhage over vertex of brain associated with thrombosis of longitudinal sinus and cortical veins. Patient died post partum. (Reproduced by courtesy of *Brain*)

Cortical venous thrombosis may be accompanied by massive subarachnoid hemorrhage shortly after onset.[13] Hemorrhage from this source may wrongly be regarded as aneurysmal in origin unless it is realized that cortical venous thrombosis is the most likely cause of subarachnoid hemorrhage in the puerperium. The brain from a patient who was thought clinically to have a ruptured berry aneurysm is shown in Figure 4.

Massive hemorrhage into cerebral tumors is uncommon.[1] In our autopsy records, there are only 15 cases in which this had occurred, 7 of these being metastatic tumors. In 5 instances, hemorrhage was the first indication of the presence of the tumor, 2 of these being metastatic. Figure 5 shows the lesion in one of the latter cases. The patient, previously healthy, suddenly collapsed with right hemiplegia four months before death. Three months later, after initial improvement, she began

having epileptic seizures and, after one of these, she died. The presence of malignancy had not been suspected until it was revealed at autopsy. In 3 other cases, the existence of the tumor had not been suspected before death, although mild symptoms had preceded the hemorrhage in each instance. In the remaining 7 cases, tumor had been diagnosed and hemorrhage was only an incident in the course of the illness, although usually followed rapidly by death.

SUMMARY

Some aspects of nonaneurysmal spontaneous intracranial hemorrhage have been discussed briefly. Attention is drawn to the existence of nonfatal cerebral hemorrhages in hypertensive cerebrovascular disease which may simulate cases of vascular insufficiency, thus leading to injudicious use of anticoagulant therapy.

Intracranial hemorrhage is the most common manifestation of angiomatous malformations and may result from very small lesions of the type that is occasionally found incidentally at autopsy. Such lesions may be largely, or even totally, destroyed by the hemorrhage and could thus account for many spontaneous intracranial hemorrhages in young persons, the cause of which has not been identified.

Brief reference is made to massive intracranial hemorrhage occuring with blood dyscrasias, cortical venous thrombosis, and intracranial neoplasms.

The author wishes to thank Professor J. Olszewski for allowing full access to the records in the Department of Neuropathology.

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General discussion of third session, May 1, 1960

Dr. Guy L. Odom, Chairman

DR. ODOM: We will now take the questions from the floor, and I will ask Dr. Baker if he will start the discussion.

DR. R. BAKER: The question was, "What are the criteria used to distinguish between transient ischemic attacks and minute cerebral infarctions with the usual postinfarction resolution from perifocal edema?"

We have no means of distinguishing these. These are pathologic differentiations. What we have done is establish a neurologic syndrome, attributable to a vascular lesion, which clears completely or nearly completely within a twelve-hour period.

DR. FISHER: The first question was, "Was age a factor in increasing the incidence of bleeding in the anticoagulative group?"

It was not in our study.

"Would you tell us the statistical significance of the difference between the results in the treated and untreated cases with transient ischemic attacks, the so-called P-values?"

Professor Munch, our statistical adviser, said it was probably significant at the 1% level, if our method of computing transient ischemic attacks was reliable.

"Does Dr. Fisher mean to imply that he can make a diagnosis in the stroke syndrome without an arteriogram?"

I think that, with a careful clinical inquiry and examination, I could come pretty close to the diagnosis in a large percentage of cases, probably higher than if I used arteriography blindly. But, at the same time, I should say that, when I have examined a patient carefully clinically and have made up my mind as to what is ailing him, to see an arteriogram or several arteriograms is always extremely enlightening and surprising to me. It may not change the diagnosis, but it always gives me a much more complete idea of the patient's illness. I don't use arteriography routinely by any means, but I am always glad to look at other persons' films.

"How long would you continue anticoagulant therapy after institution in the insufficiency syndrome?"

I know no answer to that. I have been using the rule of thumb of eight to twelve weeks, and I then stop anticoagulants. If they get into trouble again, I restart anticoagulants.

DR. ODOM: We have a question directed to Dr. Baker. "Did all your patients have angiography as in the English series?"

DR. R. BAKER: No, they did not. We feel this certainly would be a revealing type of study, but we still have not settled in our minds that this is such a benign procedure that we should do it in all such cases. We feel that the clinical diagnosis can establish whether the patient has a cerebral infarction.

DR. MARSHALL: There is a question as to what I meant by the broad spectrum of cerebrovascular disease.

In this context, I merely meant a nonembolic cerebral infarction in any site, in either the carotid or basilar territory and irrespective of whether there had been one or many attacks before. We did not distinguish among various subgroups such as patients who had recurrent transient ischemic attacks as against patients who had one single attack.

DR. GROCH: I have two questions. "From a pathologic and physiopathologic point of view, what is a thromboembolic phenomenon?"

By that, we mean occlusive disease with resultant pathology such as myocardial infarction, pulmonary embolus, or recurrent stroke.

The second question I don't believe I can answer either. "It is apparent that the incidence of hemorrhagic complications in anticoagulant patients with cerebrovascular disease

is significantly greater than in patients treated with anticoagulants because of myocardial infarction. Age difference is probably a factor, but have any other factors such as liver function impairment been determined?"

We have carefully studied renal and liver functions in the patients we have seen and have not come up with any answer. I can say that in a goodly number, perhaps over 50% of the patients who have been bleeding on long-term anticoagulant therapy in our series, we have been able to find an underlying lesion in the form of malignancy, duodenal ulcer, or hemorrhagic cystitis, which may very well explain why these persons bleed.

DR. R. BAKER: I would like to comment on Dr. Groch's figures and also to mention that, in our deaths due to hemorrhagic complications, we had only one instance where the prothrombin time was unduly extended. We had also one death due to hemorrhage where the patient had malignant hypertension with a diastolic pressure of over 130. In error, therapy had not been discontinued. His blood pressure was within a much lower range at the time of randomization. At autopsy, he had a multifocal massive hemorrhage. This then brings us down to a figure for hemorrhagic deaths, one in the control and two in the treated group, which is not a great difference. We attribute our good fortune with regard to major hemorrhagic complications to the extremely meticulous detail we have gone through to insure that prothrombin laboratory procedure is uniform and accurate.

I would like at this point to say something about the difficulty in reporting prothrombin percentages and the time in seconds, because what sounds contradictory is not necessarily so. According to our prothrombin curve, 2 to 2½ times the control in seconds in our laboratory is between 10 and 20% in all of the VA laboratories. It would help a great deal to see in reports of large studies a prothrombin curve to illustrate the range we are speaking of when we are trying to convert between seconds and percentages.

I too am troubled, as was your questioner, Dr. Groch, about categorizing and computing of thromboembolic phenomenon. We have tried to understand the difference in the frequency in our study as compared with that reported from your group. Perhaps the difference in our method of reporting reflects part of this problem. We have been reporting, as you heard today, patients with problems. We believe patients in this group are so different, one from the other, that they ought to be, for the time at least, considered independently—that is, not just group all the events together but consider how many patients have recurring events for comparison. Perhaps our figures are misleading to you when you commented about the difference, in that we have obscured the frequency of recurrence by only reporting the number of patients that have episodes rather than total number of episodes.

The other thing I wanted to mention is that we have 5 patients in our treated group who had myocardial infarctions while they were in an adequate therapeutic range, that is, between 10 and 20%, or between 2 and 2½ times the control prothrombin time in seconds.

DR. GROCH: Perhaps I should have made it more clear to the audience that we are talking in terms of patients who had recurrent episodes. In fact, some of these individuals have had several episodes, but we have not totaled them up as such, so that there is still a disparity which I do think is perhaps related to time—I don't know. Perhaps we will have an answer a year or so from now. As for myocardial infarctions occurring while the patients are theoretically within therapeutic range, yes, they occur. We see them, and everybody sees them. We all agree that we by no means have the perfect therapeutic tool for the treatment of thromboembolic diseases. If we did, we would not have this meeting today.

DR. ODOM: I think we all agree with that. There are two questions that I would like to direct to the panel.

"What danger exists in discontinuing anticoagulation?"

And another question is, "Is it generally believed that anticoagulation therapy must be continued indefinitely?"

DR. GROCH: I can say that we have had patients in whom anticoagulant therapy has been suddenly discontinued by our house staff, either by letting the prothrombin time come down to normal without the use of vitamin K_1

or when vitamin K_1 has been given because the house staff believed that they were dealing with a life-threatening situation, aside from the cerebrovascular disease, which contraindicated anticoagulants. A small number of these patients have had a repeated stroke within a period of twenty-four to forty-eight hours. We don't have any laboratory evidence that there is a rebound phenomenon. I don't think that we have the clinical technics for studying this yet. This is just a clinical impression. Rightfully or wrongfully, our group discontinues anticoagulant therapy gradually over a period of weeks. When does one stop anticoagulant therapy? I don't know the answer to this any more than anybody else does.

DR. R. BAKER: I would like to ask one question of the panel, and I will preface it by giving my impression. The question is "What will we now, on the basis of the evidence to date, recommend to our colleagues who are confronted with the difficult decision as to what to do about patients with strokes, and what are we to recommend from the evidence that we have reviewed here today?"

It is the impression of the VA Study Group that the enthusiasm for anticoagulation has caught us a little too strongly and that the application of this mode of therapy should be restricted until we have more evidence as to its efficacy, particularly, as we have all pointed out, when faced with the ever-present risk of hemorrhagic complications. At the moment, it would be my inclination only to recommend it in patients who were incapacitated by recurrent ischemic attacks, even refraining from treating with anticoagulation a person who has had one or two minor ischemic episodes. If they have many episodes before you see them, perhaps it would be well to institute therapy on the basis of the excellent information from the Mayo Clinic and Boston.

DR. GROCH: This question has been asked, "Can you state that it is significant that 50% of patients with large vessel occlusions have had previous episodes of transient ischemia when it is not known how many individuals have had episodes of transient ischemia without developing either occlusion or signs?"

As I stated when I was at the rostrum, and I hoped that Dr. Fisher would be here to answer that question, when I first see a patient, it is impossible for me and probably for most physicians to say which patient is going to be the one with transient ischemic attacks who goes on to difficulty. Perhaps by following a large group of patients and analyzing their records, one can come up with a definitive st..tement. It is important to realize that there is often a period of transient intermittent ischemia in patients with strokes and that is the time to treat them.

DR. GURDJIAN: In answer to the question concerning the number of cases operated in our group of 800 patients, there were 167 with partial occlusion or stenosis and, of these, 36 or about 5% were operated upon. In these 36, an intimectomy or intimectomy-like operation was performed. Now, there were in that group of 800 patients 78 with complete occlusion, and in this group a portion of the internal carotid artery was excised as well and a cervical sympathectomy was performed in 26 out of 42 cases. A cervical sympathectomy for this condition to help increase the communications between the external carotid artery and the internal carotid circulation, in our hands, has not been promising. Occasionally, you do see some unusual results soon after the operation. In this entire group, there were 3 examples of patients who had exploration and intimectomies of the vertebrals. In 1 patient, the vertebral was too small to do anything. In the other 2, an intimectomy was performed. In our hands, the intimectomy-type of operation has been indicated in about 5% of patients or less, and it seems to us that we are doing fewer of them as we know more about the total circulation.

DR. DE BAKEY: There are several questions here of a similar nature that I can answer best by showing two slides that I wasn't able to show previously. This is in answer to the question relating to how we maintain circulation during an operation for carotid lesions. In the upper slide, you will notice the pressure recording showing the grading of pressure in the common carotid artery and in the internal carotid artery distal to the occluding clamp. As you can see, there is a marked reduction in the pressure. This is taken from an actual case. In the lower portion of the slide, you will see

the utilization of what we call the internal shunt procedure. This consists of a small plastic flexible catheter that is inserted into the internal carotid around the clamped-off portion and into the common carotid artery and isolated so as to maintain circulation through this vessel during the time that the segment is operated upon. You can see that the pressure gradient now has been restored to normal with the catheter in place. This we regard as the best means by which circulation can be maintained. We use hypothermia no longer—we did earlier—and we do not perfuse the brain.

The next slide illustrates an analysis of our 208 patients, showing the multiplicity of involvement. You will notice that in both the complete and incomplete and combined groups, we have divided them into involvement of 1, 2, 3, and 4 or more vessels—the 4 or more are of course related to more than one lesion present. For example, lesions may be present in the arch of the aorta as well as distally. A little less than half the total number of patients had only a single artery involved. We believe this is of significance in terms of the effect of these lesions upon the collateral flow in the distal arterial bed. When more multiple lesions are present, collateral flow is less likely to be improved.

"Do you outline the intracranial vessels routinely?"

We have learned from our own experience that it is extremely important to outline the entire system if you are going to decide upon patients for surgery. Both the proximal, that is, the extracranial, and intracranial vascular systems must be visualized. The presence of intracranial occlusive disease in association with extracranial occlusive disease constitutes, in the great majority of cases, a contraindication to operation.

"Will you discuss the reason why some 400 of your patients were excluded from surgery?"

In general these exclusions are based upon the fact that there was intracranial occlusive disease. In addition, there were a certain proportion of patients who had systemic disease of other sorts that excluded operability.

"What percentage of patients fail to demonstrate back-bleeding in the carotid artery after endarterectomy?"

Virtually none, because we have learned not to operate upon that type of patient. In our early experience, we did operate upon a certain proportion of complete occlusions of the internal carotid artery of relatively long duration, that is, a matter of months or even more than a year. This, as far as we are concerned, constitutes a contraindication to operation since none have proved amenable to restoration of flow through the artery.

"What is the material used for patch graft?"

A fine knitted type of Dacron material.

"Are the patients given anticoagulants postoperatively?"

Not during their hospitalization. We do not object to the use of anticoagulants after they leave the hospital if their local physician believes they should be maintained on anticoagulant therapy.

"Among your late follow-ups, what percentage of patients were maintained on anticoagulants after surgery?"

I cannot answer that specifically, but I can tell you that it is a relatively small percentage. I would say it is in the neighborhood of 25%. We have not recommended the use of anticoagulant therapy.

"What are the dimensions or criteria for significant narrowing at the proximal portions of, or origins of, vertebral and carotid arteries?"

We made an effort to study this problem, and I am sorry that I did not have time to show two slides which illustrate our findings. In general, they are as follows: We attempted to measure from the arteriographic studies the degree of occlusion. Admittedly, this is relatively crude but, none the less, is the best approach we had. At the time of operation, we measured the pressure proximal and distal to the lesion. We found that a significant degree of difference occurred in the pressures only if the measurements demonstrated a lumen constriction of more than 50%. This, I think, is supported by experimental observations which would indicate that blood flow through a vessel is not significantly diminished until the lumen is reduced to 50% or less. This now constitutes a reasonably good criterion, as far as we are concerned, in determining whether a lesion is clinically significant.

"Do you think that extremely tortuous carotids can in certain positions cause a stroke

syndrome? Also, is surgery indicated in these cases?"

Well, it has been reported and observed. I personally have not encountered this syndrome.

"How soon after your surgery do you do your postoperative arteriograms?"

Of course, sometimes immediately after the operation, that is, on the operating table if we are not quite satisfied with the operative result. We have used pressure gradient determinations to help determine this, so that it is usually not necessary to do postoperative arteriograms on the operating table. It may be done after the operation. We usually try to do it before they leave the hospital, usually within a day or so, and that usually means within ten days of the operation. We then try to get them back in six months to a year to do postoperative arteriograms.

MR. WALSH: My first question reads, "Explain Category A and B again."

Category A patients were those who we believed were in danger of dying from the hemorrhage which had led to their admission to the hospital. These patients were in coma or stupor, and some of them had marked evidence of hemiplegia.

Category B patients were those who had recovered completely from the hemorrhage which had led to their admission to the hospital or had recovered in part with residual neurologic signs. They did not appear to be in danger of dying from the hemorrhage. In these we believed that the only risk was that of recurrent hemorrhage.

"Did you measure pressures in the carotid before and after ligation?"

No, we relied on carotid compression to determine whether the ligation would be tolerated. Most of the complications occurred two, three, and four days after ligation.

"Was the internal or common carotid artery ligated?"

The common carotid artery was ligated in one stage, no temporary or progressive occlusion being used.

"What do you do in cases of recurrence of aneurysmal bleeding after carotid ligation?"

In the series, no recurrences of bleeding have taken place, but I have seen 2 or 3 recurrences of bleeding from aneurysms in this region after carotid ligation, that is, in the region of the posterior communicating artery in some 200 or more cases. In these cases of recurrence, we restudied the patient, repeated the angiogram, and did a direct attack by clipping the neck of the aneurysm.

"How do you treat aneurysms located above the internal carotid bifurcation?"

Middle cerebral aneurysms we treat by direct attack and either clip the neck of the aneurysm or wrap the aneurysm to reinforce its wall. In the last two or three years, I have used ordinary cotton gauze quite often to wrap and reinforce the wall of the aneurysm. I believe that this affords good protection against further hemorrhage.

Anterior communicating aneurysms or aneurysms in the region of the anterior communicating artery have been treated by the clipping of that part of the anterior cerebral, proximal to the aneurysm, if there was suitable collateral circulation. If there was not adequate collateral circulation, as shown on the angiogram with compression pictures, we did a direct attack on the aneurysm, clipping its neck. Up to the present, the results of surgical treatment in these cases, the anterior communicating artery aneurysms, have not shown any great difference as compared with those in the nonsurgical group, but the study continues.

The terminal carotid aneurysms we treat by direct attack and distal anterior cerebral aneurysms by direct attack with clipping or wrapping of the aneurysm.

"Do you operate on aneurysms of the vertebral and basilar system, and what procedure do you use?"

We do not usually operate on these aneurysms. There have been one or two in the series and upon these we have performed a direct attack by clipping the neck of the aneurysm or wrapping it, as indicated.

DR. ODOM: Mr. Walsh, I would like to ask one question: What type of ligation do you use for the carotid artery?

MR. WALSH: We use an ordinary silk suture and ligate the common carotid artery just below its bifurcation. We doubly ligate it separately with silk tie immediately. Progressive occlusion of the artery was not used.

DR. ODOM: I think the incidence of complications is rather high in carotid ligation. We

are very much interested in this problem, and I would like to take this opportunity to say just a few words about it.

We use the Crutchfield clamp with gradual occlusion of the common carotid artery. We have been very much interested, as you have heard from Dr. Heyman, in pressure readings in the internal carotid artery and also the retinal pressure and intracranial pressure readings. We began our interest in the pressure studies and the use of a clamp in the neck several years ago. We would place a clamp on the common carotid artery and gradually occlude it, taking pressure readings before the clamp was applied and then with gradual occlusion of the vessel, so that we would know how many turns it would take to lower the pressure in the internal carotid artery and how much of a drop we would obtain with complete occlusion. I think that it is extremely interesting that you have to rather markedly occlude the common carotid artery before you actually begin to get a drop in the pressure in the internal carotid artery, and then you get a rather marked drop in the pressure.

We follow these patients with retinal pressure readings to determine when this pressure drop is beginning. We also auscultate the neck to determine whether a bruit appears. We have done electroencephalographic studies on some of the cases—not as many as we would like. We have found that a definite drop in the pressure in the internal carotid artery persists after occlusion. In a period of a week or ten days after we have completely occluded the common carotid artery, neck vessels have been exposed at the same time an intracranial approach was carried out. The pressure readings in the internal carotid artery intracranially, as well as in the middle cerebral artery, are still about the same as those in the internal carotid artery when we originally occluded the common carotid artery.

We brought these patients back to our aneurysm clinic. We repeated arteriography, pressure readings, and pressure studies on all of these patients as a matter of follow-up. We have changed our method of thinking as to the proper handling of intracranial aneurysms of the internal carotid artery because of the results of pressure studies and have been treating most of the patients with aneurysms of the internal carotid artery with gradual ligations of the common carotid artery. Yesterday, the comment was made that pressures in the internal carotid and the retinal artery do stay down. In the patients that have had only neck ligations and who had repeat arteriography from a month to a year and a half later, to determine what has happened to the aneurysm, we are able to get not only retinal pressure readings but also pressure readings from the internal carotid artery while they are in the X-ray department, when the needle was inserted for the arteriogram. All of the pressures have remained down in the internal carotid artery, as well as in the retinal artery. There has been some slight variation between the retinal pressure readings and the readings in the internal carotid artery. The retinal pressure may be slightly higher, but it is much lower than on the opposite side.

There is one other point that I would like to make on this particular problem as far as carotid ligation is concerned. We have always assumed that, if a patient has hemiplegia or grave neurologic deficit after the common carotid artery has been completely occluded, that patient will have a thrombosis of his internal carotid artery. This is not always true. We are doing the following at present: we never completely occlude the clamp on a common carotid artery except the very first thing in the morning. We do this because we have had patients who first showed neurologic deficits as long as ten and twelve hours after the common carotid artery has been completely occluded. If these patients are watched very closely and the clamp is opened at the first sign that they are having neurologic difficulty, they will within a matter of four or five minutes regain normal function. This has averted, I think, a thrombosis of the internal carotid artery which surely would have resulted had the clamp been left completely closed.

There is more to this problem, I think, than whether pressures stay down. A major question is whether a patient will be asymptomatic after a neck ligation and, when he has a repeat arteriogram, the aneurysm may still be visualized off the internal carotid artery. It may not be as large as it was at the time of the first arteriogram. We have observed a change in the size of an aneurysm in a period

of two weeks and have failed to see any additional change after a year. Whether an aneurysm is still going to be subject to repeated bleeding later on, I do not know.

I would like to make one other comment. I think the studies that are being carried out at the present time, sponsored by the Veterans Administration and by the U.S. Public Health Department, are the only methods that we are going to have to arrive finally at some definite decision as to whether anticoagulants should be used in stroke and whether some approach should be made to the extracranial vessels, and whether we should operate on intracranial aneurysms by an intracranial approach or by an extracranial approach or leave them alone and not do anything except follow them with bedrest. The literature over the last hundred years is not valuable at all as far as mortality or morbidity from aneurysms is concerned because all of the statistics are based on the findings of intracranial or subarachnoid bleeding. As has been pointed out by Dr. Hyland, there are causes of subarachnoid bleeding other than aneurysms. Aneurysm carries a much higher mortality and a much higher morbidity than some of the other causes.

Another important point is the fact that you can have intracranial bleeding without blood in the subarachnoid space. In patients with suspected intracerebral bleeding in whom the arteriogram is negative, we think that air studies are justified, especially in those cases in which the intracerebral bleeding is suspected to have occurred in the parietal or parietooccipital region.

I would again like at this time to mention the small angiomatous malformations, and I think that, as physicians continue to look for them, they will find that there is an abnormality in the wall of the hematoma which was responsible for the spontaneous intracerebral bleeding.

Dr. Sahs, when is the public health study expected to be published?

DR. SAHS: We will probably continue this study for the next two or three years, and publication will necessarily be delayed until we receive what we feel is an adequate series.

DR. ODOM: The following question was directed to me, "Are follow-up angiograms carried out in carotid ligation cases? If so, would you comment on the patency or lack of it in the carotid—also the state of the aneurysm?"

I have answered the part about the aneurysm. I think in our group, so far, only about one-fifth of the aneurysms have failed to visualize in repeat arteriography up to a year or a year and a half later. The internal carotid artery has been thrombosed in a very small percentage of cases; I can't tell you exactly how many. Even though thrombosis has occurred in the internal carotid artery after ligation of the common carotid artery, there have been no neurologic deficits.

The next question is for Mr. Walsh, "With what frequency have you seen delayed (that is, for several days) onset of cerebral lateralizing signs in patients with ruptured intracranial aneurysms? Would you list the mechanisms for such delayed cerebral infarcts complicating hemorrhage from ruptured aneurysm?"

MR. WALSH: I presume this means in surgically treated patients. We have seen this, and, in the 150 conservatively treated patients that we have in the series so far, it has happened on 3 occasions that such a delayed onset of cerebral lateralizing signs has taken place without evidence of recurrent subarachnoid hemorrhage. I think the most common cause of such delayed lateralizing signs is recurrent hemorrhage. Of 3 patients in whom we did not think hemorrhage had recurred, 1 had a repeated angiogram which showed that several of the branches of the middle cerebral artery, which had previously been visualized some ten to fourteen days earlier, were no longer visualized and we thought that there had been an occlusion. We have also repeated angiograms in these patients and other patients showing similar signs. These have shown marked spasm or narrowing not previously present. None had evidence of recurrent hemorrhage in the cerebrospinal fluid.

DR. GROCH: "Is there any rationale for the use of anticoagulant therapy in basilar artery syndromes, as contrasted to other cerebral vessels? If so, why?" I would assume that this refers to the carotid tree.

There is a difference in the prognosis for patients who have basilar-vertebral disease as contrasted to carotid disease. I don't think that we can make any definitive statements

that anticoagulants are definitely indicated in one type of disease as contrasted to the other at this time. I think we can say that anticoagulant therapy does seem to decrease the incidence of transient ischemic episodes, whether they occur in either tree. It would seem that transient ischemic episodes associated with basilar-vertebral disease carry a worse prognosis and, therefore, provide the rationale for using anticoagulants in that type of disease.

"What are the criteria that have led to the stipulation of a therapeutic range of prothrombin times of from 2 to 2½ times the control?"

The answer is experience. We have learned that persons with a prothrombin time above, say, 35 to 40 sec., when the control is 14 to 15 sec., are likely to get into trouble. Dr. McDevitt has a considerable amount of data now which show that, if you maintain the prothrombin time below 22 sec. and probably 25 sec., there will be a greater tendency for thrombosis. The answer to this question is experience, particularly with diseases other than cerebrovascular disease.

"In patients with transient ischemic attacks receiving anticoagulant therapy, is there a difference in clinical response, that is, in preventing further attacks or more serious complications, if the lesion is extracerebral or intracranial?"

There is no answer at this time.

"Since transient ischemic attacks respond to anticoagulants, does this mean [1] decreased blood viscosity, [2] increased cerebral blood flow, or [3] both?"

I don't think there is a clear answer to this either. I do think that Dr. John Meyer's experimental work shows that anticoagulant therapy does tend to prevent "sludging" of blood in the collateral circulation.

This question was directed to Dr. Fisher, "Have you seen any delayed hemorrhages, for example, in the liver after cessation of anticoagulant therapy, say, four to five days or one week later with normal prothrombin times?"

I would say no. I think Dr. Baker has some comments he would like to make.

DR. R. BAKER: Concerning the problem of prognosis in basilar thrombosis, the picture has been painted rather dark about disease in this artery, and yet in our study we have not seen any significant difference in the prognosis in the two groups, either in the controls or treated patients. We are coming to believe that, perhaps, with further information about the natural history, thrombosis in the vertebral-basilar tree is not truly too much worse in its prognosis than thrombosis in the carotid tree.

I want to state that we have seen few hemorrhagic problems of the diffuse sort that you might think you would encounter. Almost all of our bleeding patients have had some basic pathologic condition at the site of bleeding and have not shown diffuse hemorrhagic phenomena.

One question that was also passed up to me was, "Were not patients as often out of control or likely to be out of control in the under-anticoagulated as in the over-anticoagulated range, and wasn't that dangerous or a problem?"

A portion of our patients did have prothrombin times not elevated to an adequate therapeutic level, by our definition, but these patients did not seem to fare any differently, as far as we have analyzed the data, than the others. The course of the whole group is so relatively benign. These patients did not have their trouble because of falling below the desired anticoagulant range.

I wanted to comment that our group has been impressed by how well these patients do in a clinic where they are given attention and interest. These patients are a very happy group and are very cooperative, and we have been impressed how nicely they do whether they receive treatment or not.

One other question that came up, "How frequently do ischemic attacks precede infarctions?"

We hope that, out of the several studies presented here, we will be able to add something to our information about that. Actually, to date, very few of our patients who have had infarcts have had preceding ischemic attacks.

DR. MARSHALL: The only other point that I would like to make about the difference between the basilar and the hemisphere lesions is the possibility that it is easier to overlook a small hemorrhage in the hemisphere than it is in the basilar territory. I think a great problem of anticoagulant therapy is the small hemorrhage that one has failed to diagnose.